N-SUBSTITUTED PIPERIDINE AND PIPERAZINE DERIVATIVES

BACKGROUND OF THE INVENTION

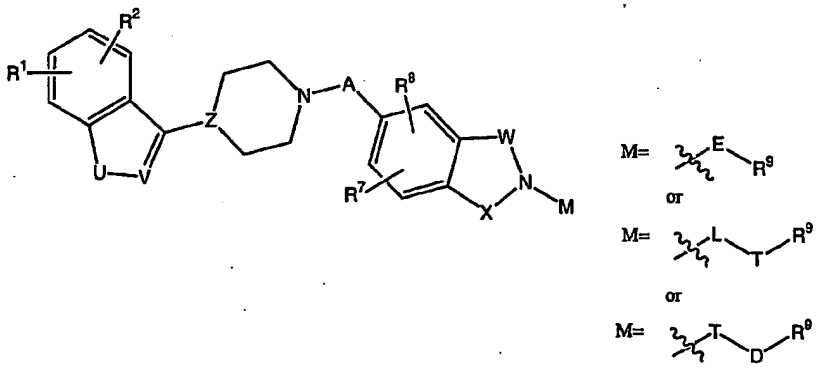
This invention relates to N-substituted piperidine and piperazine derivatives, pharmaceutical compositions containing them and their use for the treatment of schizophrenia and other central nervous system (CNS) disorders or conditions. The N-substituted piperidine and piperazine derivatives of this invention exhibit activity as antagonists of dopamine D2 receptors and of serotonin 2A (5HT2A) receptors.

Other heterocyclic piperazine derivatives that are useful for the treatment of schizophrenia are referred to in United States patent 5,350,747, which issued on September 27, 1994, and in United States patent 6,127,357, which issued on October 3, 2000. These patents are incorporated herein by reference in their entirety.

Other piperazine and piperidine derivatives that have been stated to be useful as antipsychotic agents are those referred to in PCT patent publication WO 93/04684, which published on March 18, 1993, and European patent application EP 402644A, which was published on December 19, 1990. These patent applications are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention relates to compounds of formula **1**



wherein

U is sulfur, oxygen, SO, SO_2, CH_2 or NR^3;

V is nitrogen or carbon;

Z is nitrogen or carbon;

A is $-(CH_2)_mO-$; $-(CH_2)_mNR^4-$; or $-(CH_2)_mC(R^5R^6)-$, wherein R^5 and R^6 are independently selected from hydrogen, (C_1-C_4) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_4) alkoxy optionally substituted with from one to three fluorine atoms, hydroxy, and aminoalkyl; or R^5 and R^6 together form a carbonyl, and wherein m is an integer from one to four;

R^1 and R^2 are independently selected from hydrogen, (C_1-C_4) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_4) alkoxy optionally substituted with from one to three fluorine atoms, halogen, nitro, cyano, amino, (C_1-C_4) alkylamino and di-(C_1-C_4) alkylamino;

R^3 and R^4 are independently selected from hydrogen, (C_1-C_4) alkyl optionally substituted with from one to three fluorine atoms and (C_1-C_4) alkoxy optionally substituted with from one to three fluorine atoms;

or, when U is NR^3, one of R^1 and R^2 can form, together with the carbon to which it is attached, and together with R^3 and the nitrogen to which it is attached, a heterocyclic ring containing from four to seven ring members of which from one to three ring members can be heteroatoms selected from nitrogen, oxygen and sulfur, and of which the remaining ring members are carbon, with the proviso that when R^3 forms a ring with one of R^1 and R^2, the other of R^1 and R^2 is absent.

X is $-[C(R^{11})(R^{12})]_o-$, wherein R^{11} and R^{12} are independently selected from hydrogen and (C_1-C_4) alkyl optionally substituted with from one to three fluorine atoms, and wherein o is an integer from zero to three, with the proviso that when W is absent, o must be greater than or equal to two;

W is $-[C(R^{13})(R^{14})]_p-$, wherein R^{13} and R^{14} are independently selected from hydrogen and (C_1-C_4) alkyl optionally substituted with from one to three fluorine atoms, and wherein p is an integer from zero to four, with the proviso that when X is absent, p is greater than or equal to two;

R^7 and R^8 are independently selected from halo, R^1 and $-OR^1$; or R^7, when attached to a carbon adjacent to one of the carbon atoms shared by both the phenyl ring to which R^7 is attached and the ring containing W, N and X, forms, together with a carbon atom of X or a carbon atom of W, a saturated carbocyclic ring containing from three to six carbon atoms;

R^9 is selected from phenyl, phenoxy, benzyloxy, and phenylamino, wherein the phenyl moieties of said phenyl, phenoxy, benzyloxy, and phenylamino are optionally substituted with from one to three substituents independently selected from halo, (C_1-C_3) alkyl optionally substituted with from one to three fluorine atoms, (C_1-C_3) alkoxy optionally substituted with from one to three fluorine atoms, nitro, cyano, amino, and (C_1-C_3) alkylamino; or

R^9 is a pyrrolidine, piperidine or morpholine ring wherein the point of attachment to D, T or E is the ring nitrogen, and wherein said pyrrolidine, piperidine or morpholine ring can be optionally substituted with one or two substituents independently selected from methyl, amino, (C_1-C_4) alkylamino, and di-(C_1-C_4) alkylamino; or

R^9 is a furan, thiophene, or pyrazole ring optionally substituted with one or two (C_1-C_4) alkyl groups; or

R^9 is (C_1-C_6) straight or branched alkyl or (C_3-C_6) cycloalkyl, wherein said straight, branched and cyclic alkyl moieties are be optionally substituted with from one to three halo atoms or (C_1-C_4) alkoxy optionally substituted with from one to three fluorine atoms; or

R^9 is halogen, nitro, cyano, amino, (C_1-C_4) alkylamino, di-(C_1-C_4) alkylamino or OR^1, wherein the alkyl moieties of (C_1-C_4) alkylamino and di-(C_1-C_4) alkylamino are optionally substituted with an amino, (C_1-C_4) alkylamino, or di-(C_1-C_4) alkylamino group;

E is -C(O)-, -S(O)- or -SO_2-;

T is -C(O)- or -CO_2-;

L is -$(CH_2)_n$ wherein n is an integer from zero to three;

D is -$(CHR^{10})_q$-, wherein q is an integer from one to three, or NR^{10};

R^{10} is hydrogen or straight or branched (C_1-C_3) alkyl;

and pharmaceutically acceptable salts thereof.

Specific embodiments of the invention include compounds of the formula **1** wherein: U is sulfur;

U is sulfur, oxygen or NR^3;

V is nitrogen;

Z is nitrogen;

A is $-(CH_2)_mC(R^5R^6)-$, wherein R^5 and R^6 are hydrogen and m is one or two;

A is ethylene or propylene;

R^1 and R^2 are independently selected from hydrogen, (C_1-C_4) alkyl, (C_1-C_4) alkoxy and halogen;

R^1 and R^2 are hydrogen;

X is absent;

W is $[C(R^{13})(R^{14})]_p$ -, wherein R^{13} and R^{14} are independently selected from hydrogen and (C_1-C_4) alkyl, and wherein p is two to four;

W is ethylene or propylene;

R^7 and R^8 are independently selected from hydrogen, chloro and methyl;

R^8 is chloro or methyl;

M is $C(O)R^9$ and R^9 is (C_1-C_4) alkyl;

M is ER^9, E is -C(O)- and R^9 is (C_1-C_4) alkyl;

M is ER^9, E is -C(O)- and R^9 is optionally substituted phenyl or optionally substituted phenoxy; or

M is TDR^9, T is -C(O)- and R^9 is optionally substituted phenyl or optionally substituted phenoxy.

Examples of specific embodiments of this invention include the following compounds and their pharmaceutically acceptable salts:

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone;

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone;

1-{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-ethanone;

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-3,3-diethyl-2,3-dihydro-indol-1-yl}-ethanone;

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone;

1-{6-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-3,3-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone;

1-{6-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-7-fluoro-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone;

1-{6-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone;

1-(7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone;

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-2-pyrrolidin-1-yl-ethanone;

3-(4-{2-[1-(4,5-Dihydro-oxazol-2-yl)-2,3-dihydro-1H-indol-5-yl]-ethyl}-piperazin-1-yl)-benzo[d]isothiazole;

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydro-isoindol-2-yl}-propan-1-one;

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2,2-dimethyl-propan-1-one;

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-(3-dimethylamino-pyrrolidin-1-yl)-ethanone;

1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2H-quinolin-1-yl}-ethanone;

1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-propan-1-one;

7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1-propyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine; and

1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-2-methyl-propan-1-one.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl", unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof. Examples of "alkyl" groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, iso- sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and the like.

The term "alkoxy", unless otherwise indicated, means "alkyl-O-", wherein "alkyl" is as defined above. Examples of "alkoxy" groups include, but are not limited to, methoxy, ethoxy, propoxy, butoxy and pentoxy.

The term "alkenyl", unless otherwise indicated, includes unsaturated hydrocarbon radicals having one or more double bonds connecting two carbon atoms, wherein said hydrocarbon radical may have straight, branched or cyclic moieties or combinations thereof. Examples of "alkenyl" groups include, but are not limited to, ethenyl, propenyl, butenyl, pentenyl.

The term "one or more substituents", refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites.

The terms "halo" and "halogen", unless otherwise indicated, include, fluoro, chloro, bromo and iodo.

The compounds of formula **1** and their pharmaceutically acceptable salts are also referred to herein, collectively, as the "compounds of this invention" and the "active compounds of this invention".

This invention also relates to a pharmaceutical composition comprising a compound of formula **1** and a pharmaceutically acceptable carrier. Additionally, this invention relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula **1**, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Compounds of formula **1** may contain chiral centers and therefore may exist in different enantiomeric and diastereomeric forms. This invention relates to all optical isomers and all stereoisomers of compounds of the formula **1**, both as racemic mixtures and as individual enantiomers and diastereoisomers of such compounds, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment defined above that contain or employ them, respectively. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate. Individual enantiomers of the compounds of formula **1** may have advantages, as compared with the racemic mixtures of these compounds, in the treatment of various disorders or conditions.

In so far as the compounds of formula **1** of this invention are basic

compounds, they are all capable of forming a wide variety of different salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the base compound from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert to the free base compound by treatment with an alkaline reagent and thereafter convert the free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the base compounds of this invention are readily prepared by treating the base compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent or in a suitable organic solvent, such as methanol or ethanol. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts.

The present invention also includes isotopically labeled compounds, which are identical to those recited in formula 1, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation

and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of formula **1** of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of formula **1** of this invention have useful pharmaceutical and medicinal properties.

The term "treating", refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or preventing one or more symptoms of such condition or disorder. The term "treatment", refers to the act of treating, as "treating" is defined immediately above.

This invention also relates to a method of treating a disorder or condition selected from the group consisting of single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression including anorexia, weight loss, insomnia, early morning waking or psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, seasonal affective disorder and pediatric depression; bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; conduct disorder; disruptive behavior disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social anxiety, social phobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders, psychotic disorders with delusions or hallucinations, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major

depressive disorder; mood disorders associated with psychotic disorders such as acute mania and depression associated with bipolar disorder; mood disorders associated with schizophrenia; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorder, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; chemical dependencies and addictions (e.g., dependencies on, or addictions to, alcohol, heroin, cocaine, benzodiazepines, nicotine, or phenobarbitol) and behavioral addictions such as an addiction to gambling; and ocular disorders such as glaucoma and ischemic retinopathy in a mammal, including a human, comprising administering to the mammal in need of such treatment an amount of a compound of the formula **1**, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a disorder or condition selected from the disorders and conditions as defined in the paragraph directly above, in a mammal in need of such treatment, including a human, comprising an amount of a compound of the formula **1**, or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder or condition, and a pharmaceutically acceptable carrier.

A more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from major depression, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthymia, cyclothymia and bipolar disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from schizophrenia, schizoaffective disorder, delusional disorder, substance-induced psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, and schizophreniform disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from autism, pervasive development disorder, and attention deficit hyperactivity disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobias, including social phobia, agoraphobia, and specific phobias.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; and extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorder, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies.

Another more specific embodiment of this invention relates to the above method and composition wherein the compound of formula **1** is administered to a human for the

treatment of any two or more comorbid disorders or conditions selected from those disorders and conditions referred to in any of the above methods.

For the treatment of depression, anxiety, schizophrenia or any of the other disorders and conditions referred to above in the descriptions of the methods and pharmaceutical compositions of this invention, the compounds of this invention can be used in conjunction with one or more other antidepressants or anti-anxiety agents. Examples of classes of antidepressants that can be used in combination with the active compounds of this invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-1 receptor antagonists, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), corticotropin releasing factor (CRF) antagonists, α-adrenoreceptor antagonists, and atypical antidepressants. Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butripyline, iprindole, lofepramine, nortriptyline, protriptyline, amoxapine, desipramine and maprotiline. Suitable selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcyclopramine. Suitable reversible inhibitors of monoamine oxidase include moclobemide. Suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include venlafaxine. Suitable CRF antagonists include those compounds described in International Patent Application Nos. WO 94/13643, WO 94/13644, WO 94/13661, WO 94/13676 and WO 94/13677. Suitable atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine. Suitable NK-1 receptor antagonists include those referred to in World Patent Publication WO 01/77100.

Suitable classes of anti-anxiety agents that can be used in combination with the active compounds of this invention include benzodiazepines and serotonin IA (5-HT_{IA}) agonists or antagonists, especially 5-HT_{IA} partial agonists, and corticotropin releasing factor (CRF) antagonists. Suitable benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam,

oxazepam, and prazepam. Suitable 5-HT_{1A} receptor agonists or antagonists include buspirone, flesinoxan, gepirone and ipsapirone.

This invention also relates to a method of treating a disorder or condition selected from single episodic or recurrent major depressive disorders, dysthymic disorders, depressive neurosis and neurotic depression, melancholic depression including anorexia, weight loss, insomnia, early morning waking or psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypersomnia, psychomotor agitation or irritability, seasonal affective disorder and pediatric depression; bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; conduct disorder; disruptive behavior disorder; behavioral disturbances associated with mental retardation, autistic disorder, and conduct disorder; anxiety disorders such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social anxiety, social phobia, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalized anxiety disorders; borderline personality disorder; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders, psychotic disorders with delusions or hallucinations, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders such as acute mania and depression associated with bipolar disorder; mood disorders associated with schizophrenia; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorder, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic

malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; chemical dependencies and addictions (e.g., dependencies on, or addictions to, alcohol, heroin, cocaine, benzodiazepines, nicotine, or phenobarbitol) and behavioral addictions such as an addiction to gambling; and ocular disorders such as glaucoma and ischemic retinopathy in a mammal in need of such treatment, including a human, comprising administering to said mammal:

(a) a compound of the formula **1** or a pharmaceutically acceptable salt thereof; and

(b) another pharmaceutically active compound that is an antidepressant or anti-anxiety agent, or a pharmaceutically acceptable salt thereof;

wherein the active compounds "a" and "b" are present in amounts that render the combination effective in treating such disorder or condition.

This invention also relates to a pharmaceutical composition for treating a disorder or condition selected from the disorders and conditions as defined in the paragraph directly above, in a mammal in need of such treatment, including a human, comprising:

(a) a compound of the formula **1** or a pharmaceutically acceptable salt thereof;

(b) another pharmaceutically active compound that is an antidepressant or anti-anxiety agent, or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active compounds "a" and "b" are present in amounts that render the composition effective in treating such disorder or condition.

A more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from major depression, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthymia, cyclothymia and bipolar disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from schizophrenia, schizoaffective disorder, delusional disorder, substance-induced

psychotic disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to a general medical condition, and schizophreniform disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from autism, pervasive development disorder, and attention deficit hyperactivity disorder.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobias, including social phobia, agoraphobia, and specific phobias.

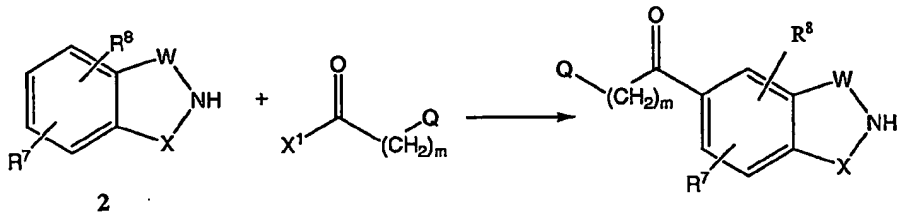
Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from movement disorders such as akinesias, dyskinesias, including familial paroxysmal dyskinesias, spasticities, Tourette's syndrome, Scott syndrome, PALSYS and akinetic-rigid syndrome; and extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced Parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour.

Another more specific embodiment of this invention relates to the above method and composition wherein the disorder or condition that is being treated is selected from delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Parkinson's disease (PD), Huntington's disease (HD), Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, memory disorder, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies.

Another more specific embodiment of this invention relates to the above method and composition wherein the compound of formula **1** and the additional antidepressant or anti-anxiety agent are administered to a human for the treatment of any two or more comorbid disorders or conditions selected from those disorders and conditions referred to in any of the above methods.

The compounds of formula **1** of the present invention may be prepared as described in the following reaction schemes. Unless otherwise indicated, in the reaction schemes and discussion that follow, R^1 through R^{14}, A, n, m, o, p, q, U, V, L, W, D, E, T, Z and X are defined as above.

SCHEME A-1

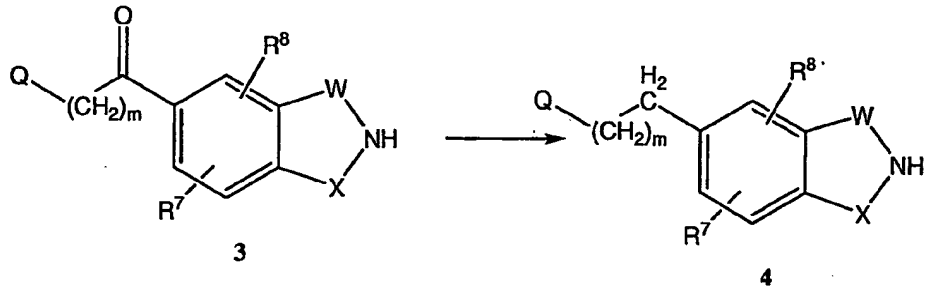


2 **3**

[In compounds **2** and **3**, one of the $-CH_2-$ groups of X or W is replaced by -C(O)-]

The above scheme illustrates a method for preparing compounds of the formula **3** by reacting a compound of the formula **2** with a compound of formula $X^1CO(CH_2)_mQ$, wherein X^1 is either a halogen or OH and Q is either a halogen, mesylate, or tosylate. When X^1 is represented by a halogen, the reaction is typically carried out in the presence of a Lewis acid such as aluminum bromide ($AlBr_3$), aluminum chloride ($AlCl_3$), gallium trichloride ($GaCl_3$), ferric chloride ($FeCl_3$), zinc chloride ($ZnCl_2$), antimony pentachloride ($SbCl_5$), zirconium tetrachloride ($ZrCl_4$), tin tetrachloride ($SnCl_4$), boron trichloride (BCl_3), boron trifluoride (BF_3), or antimony trichloride ($SbCl_3$). The reaction can be carried out in nonpolar solvents such as chloroform, dichloromethane, dichloroethane, or carbon disulfide, or in polar solvents such as nitrobenzene, or may be run neat in the presence of excess Lewis acid. The reaction is typically carried out at a temperature of 25°C to about 120°C for a period of about 1 hour to 48 hours preferably, 1 hour to 6 hours. Where X^1 is represented by OH, the reaction is typically carried out in the presence of a proton acid such as polyphosphoric acid or sulfuric acid.

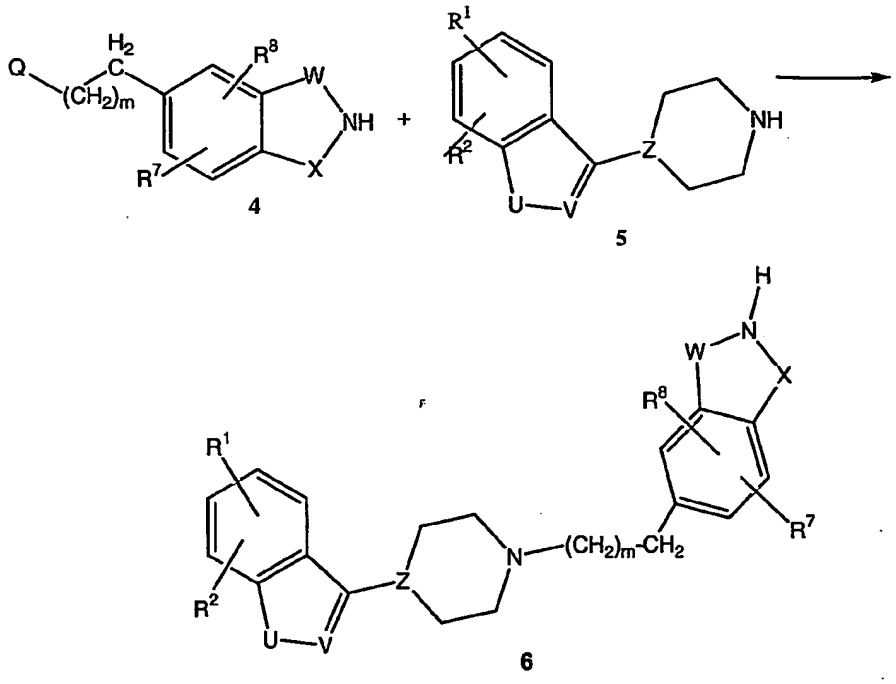
SCHEME A-2



[In compounds **3** and **4**, one of the -CH_2- groups of X or W is replaced by -C(O)-]

The above scheme illustrates a method for preparing compounds of the formula **4**. In compounds of the formulas **3** and **4**, Q is defined as it is defined above in the description of Scheme A-1. The reaction illustrated in Scheme A-2 can be carried out using triethylsilane in trifluoroacetic acid at a temperature from about rt to the reflux temperature of the solvent for a period of up to about 24 hours. Alternatively, the reaction may be carried out using borane-tert-butylamine in the presence of a Lewis acid such as aluminum chloride or by using borane-dimethylamine in the presence of a Lewis acid such as titanium tetrachloride in an inert solvent such as dichloromethane, chloroform, or nitrobenzene under temperatures described.

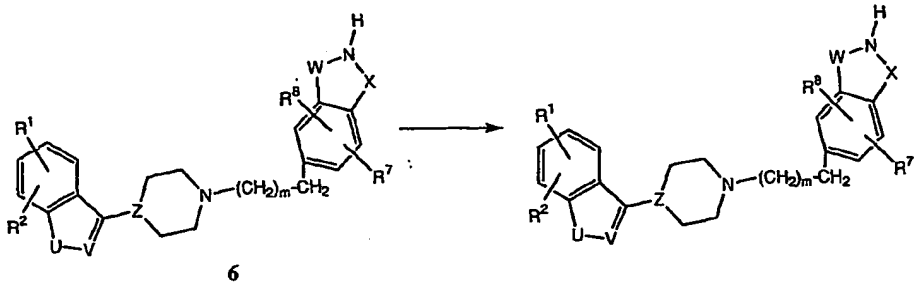
SCHEME A-3



[In compounds **4**, **5** and **6**, one of the -CH_2- groups of X or W is replaced by -C(O)-]

The above scheme illustrates a method for preparing compounds of the formula **6**, by reacting a compound of the formula **4**, as described in Scheme A-2, with a compound of formula **5**. The reaction is typically run in the presence of a base such as potassium carbonate, sodium carbonate, triethylamine, or diisopropylethylamine. The solvent used may be water, acetonitrile, dioxane, benzene, toluene, tetrahydrofuran, methyl isobutyl ketone, or a combination of two of the formerly mentioned solvents. Inorganic salts such as a sodium or potassium halide (*e.g.*, sodium iodide or potassium iodide) may be employed as catalysts in the reaction. The temperature of the reaction may vary from ambient to reflux temperature of the solvent used, preferably from about 80°C to 120°C, for a period of about 1 hour to about 96 hours, preferably from about 12 hours to 48 hours.

SCHEME A-4

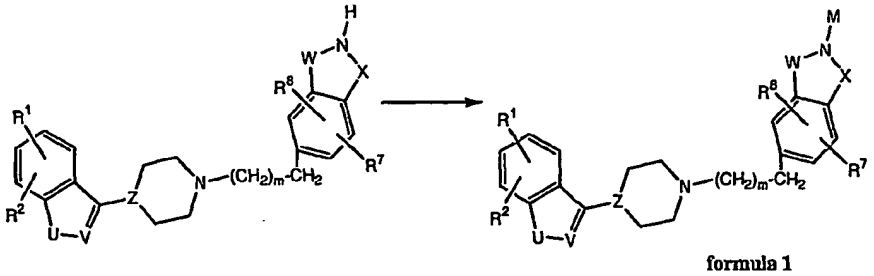


6 7

[In compound **6**, one of the $-CH_2-$ groups of W or X is replaced by -C(O)-]

The above scheme illustrates a method for preparing compounds of the formula **7** by reducing the amide carbonyl in the compound of the formula **6** with a reducing agent such as borane THF, or borane dimethyl sulfide. The reaction above can be carried out in a solvent such as methylene chloride, tetrahydrofuran, dichloroethane, benzene, or toluene. This reaction is typically carried out at a temperature from about –78 °C to about the reflux temperature of the solvent, preferably from about –20 °C to about 50 °C, for a period of about 5 minutes to about 48 hours, preferably from about 0.5 to about 16 hours. The reaction is typically quenched with methanol, water, or a dilute base such as sodium carbonate or sodium bicarbonate. Preferably, the reaction is quenched with methanol or 10% sodium carbonate and the complexes are broken up by heating the reaction mixture to a temperature from about 30 °C to about the reflux temperature of the solvent, preferably to about 90 °C, for about 0.5 to about 20 hours, preferably for about 2 hours.

SCHEME A-5

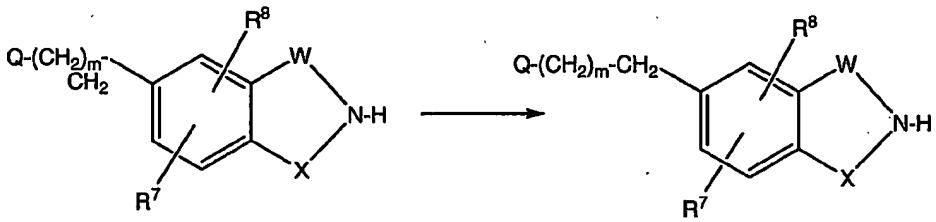


7 formula 1

The above scheme illustrates a method for preparing compounds of the formula **1** by reacting compounds of the formula **7** with a compound of the formula

R^9-G wherein G is –COCl, an acid or a suitably activated acid derivative such as the mixed anhydride, -OCOCl, -N=C=O, or -SO_2Cl, or wherein R^9-G is $ClSO_2N(Me)_2$. This reaction may be carried out in an inert solvent such as methylene chloride, dichloromethane, dichloroethane, benzene, toluene, tetrahydrofuran, or pyridine, preferably methylene chloride. Typically, it is carried out at a temperature from about –78 °C to about the reflux temperature of the solvent, preferably from about 0 °C to about 25 °C, for a period of about 5 minutes to 72 hours, preferably from about 0.5 to about 16 hours. This reaction is generally performed in the presence of organic base such as diisopropylethylamine, pyridine, or triethylamine, preferably triethylamine, or in the presence of a polymer supported base such as tris-(2-aminoethyl)amine polystyrene.

SCHEME B-1



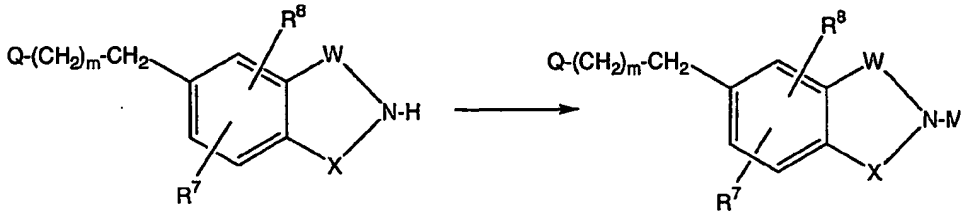
4 8

[In compound **4**, one of the -CH_2- groups of W or X is replaced by -C(O)-]

The above scheme illustrates a method for preparing compounds of the formula **8** by reducing the amide carbonyl in a compound of the formula **4** with a reducing agent such as borane THF, or borane dimethyl sulfide. The reaction above can be carried out in a solvent such as methylene chloride, tetrahydrofuran, dichloroethane, benzene, or toluene. This reaction is typically carried out at a temperature from about –78°C to about the reflux temperature of the solvent, preferably from about –20°C to about 50°C, for a period of about 5 minutes to about 48 hours, preferably from about 0.5 to about 16 hours. The reaction is typically quenched with methanol, water, or a dilute base such as sodium carbonate or sodium bicarbonate. Preferably, the reaction is quenched with methanol or 10% sodium carbonate and the complexes are broken up by heating the reaction mixture

to a temperature from about 30°C to about the reflux temperature of the solvent, preferably to about 90°C, for about 0.5 to about 20 hours, preferably for about 2 hours.

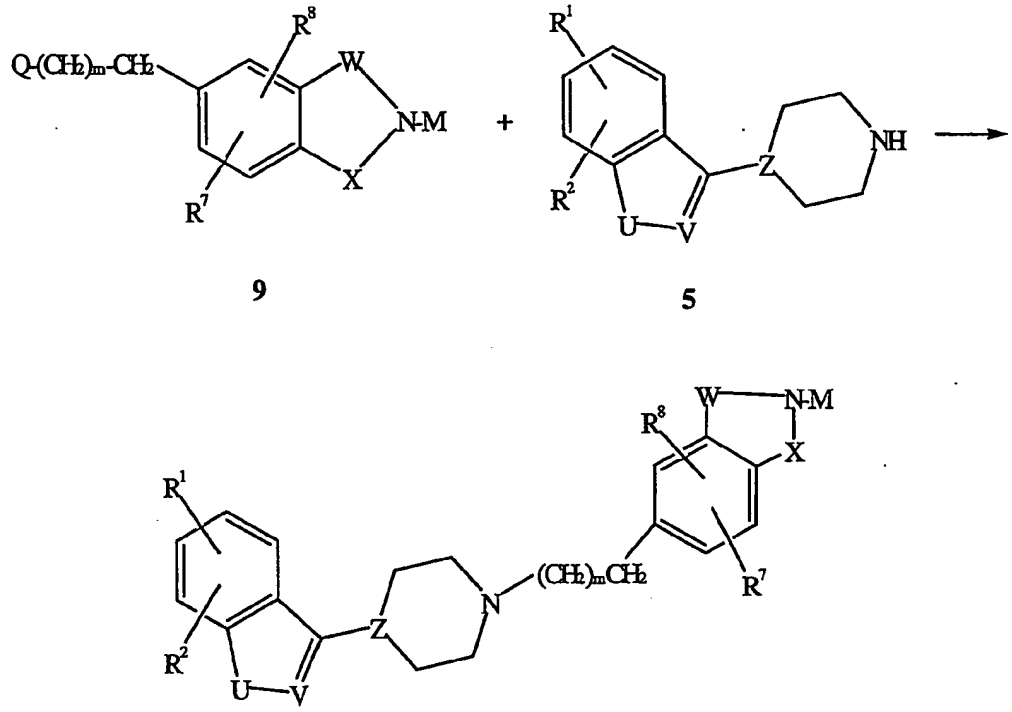
SCHEME B-2



8 9

The above scheme illustrates a method for preparing compounds of the formula **9** by reacting compounds of the formula **8** with a compound of the formula R^9-G wherein G is –COCl, an acid or a suitably activated acid derivative such as the mixed anhydride, -OCOCl, -N=C=O, or -SO_2Cl, or wherein R^9-G is $ClSO_2N(Me)_2$. This reaction may be carried out in an inert solvent such as methylene chloride, dichloroethane, benzene, toluene, tetrahydrofuran, or pyridine, preferably methylene chloride. Typically, it is carried out at a temperature from about –78°C to about the reflux temperature of the solvent, preferably from about 0°C to about 25°C, for a period of about 5 minutes to 48 hours, preferably from about 0.5 to about 16 hours. This reaction is generally performed in the presence of organic base such as diisopropylethylamine, pyridine, or triethylamine, preferably triethylamine, or in the presence of a polymer supported base such as tris-(2-aminoethyl)amine polystyrene.

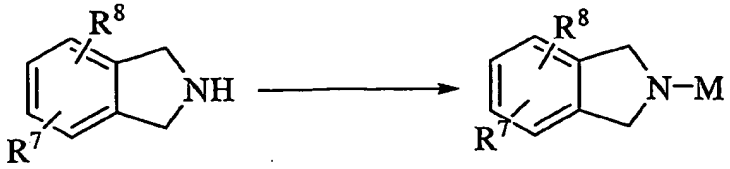
SCHEME B-3



Formula 1

The above scheme illustrates a method for preparing compounds of the formula **1** wherein A is $-(CH_2)_mCH_2-$ by reacting a compound of the formula **9**, as described in scheme B-2, with a compound of formula **5**. The reaction is typically run in the presence of a base such as potassium carbonate, sodium carbonate, triethylamine, or diisopropylethylamine. The solvent used may be water, acetonitrile, dioxane, benzene, toluene, tetrahydrofuran, methyl isobutyl ketone, or a combination of two of the formerly mentioned solvents. Inorganic salts such as a sodium or potassium halide (*e.g.*, sodium iodide or potassium iodide) may be employed as catalysts in the reaction. The temperature of the reaction may vary from ambient to reflux temperature of the solvent used, preferably from about 80°C to 120°C, for a period of about 1 hour to about 96 hours, preferably from about 12 hours to 48 hours.

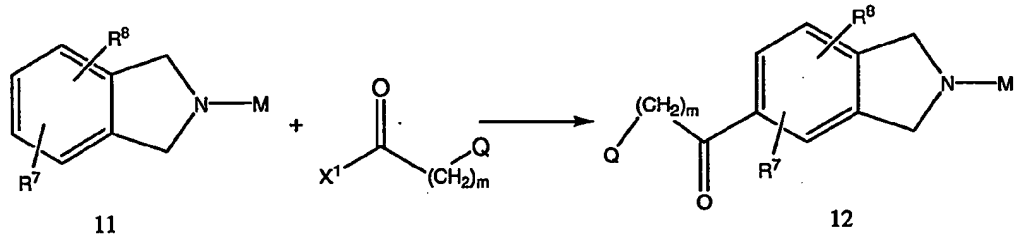
SCHEME C-1



10 11

The above scheme illustrates a method for preparing compounds of the formula **11** by reacting compounds of the formula **10** with a compound of the formula R^9-G wherein G is –COCl, an acid or a suitably activated acid derivative such as the mixed anhydride, -OCOCl, -N=C=O, or -SO_2Cl, or wherein R^9-G is $ClSO_2N(Me)_2$. This reaction may be carried out in an inert solvent such as methylene chloride, dichloroethane, benzene, toluene, tetrahydrofuran, or pyridine, preferably methylene chloride. Typically, it is carried out at a temperature from about –78 °C to about the reflux temperature of the solvent, preferably from about 0 °C to about 25 °C, for a period of about 5 minutes to 48 hours, preferably from about 0.5 to about 16 hours. This reaction is generally performed in the presence of organic base such as diisopropylethylamine, pyridine, or triethylamine, preferably triethylamine, or in the presence of a polymer supported base such as tris-(2-aminoethyl)amine polystyrene.

SCHEME C-2

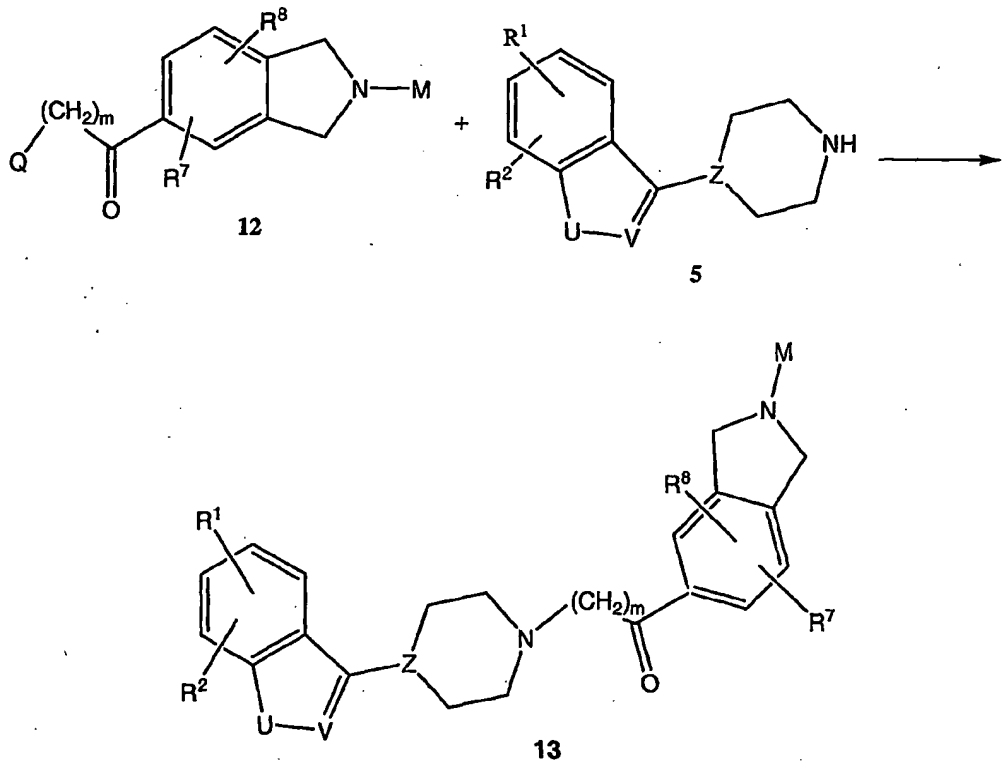


11 12

The above scheme illustrates a method for preparing compounds of the formula **12** by reacting a compound of the formula **11** with a compound of formula $X^1CO(CH_2)_mQ$, X^1 is either a halogen or OH and Q is either a halogen, mesylate, or tosylate. When X^1 is represented by a halogen, the reaction is typically carried out in the presence of a Lewis acid such as aluminum bromide ($AlBr_3$), aluminum chloride ($AlCl_3$), gallium trichloride ($GaCl_3$), ferric chloride ($FeCl_3$), zinc chloride ($ZnCl_2$),

antimony pentachloride ($SbCl_5$), zirconium tetrachloride ($ZrCl_4$), tin tetrachloride ($SnCl_4$), boron trichloride (BCl_3), boron trifluoride (BF_3), or antimony trichloride ($SbCl_3$). The reaction can be carried out in nonpolar solvents such as chloroform, dichloromethane, dichloroethane, or carbon disulfide, or in polar solvents such as nitrobenzene, or may be run neat in the presence of excess Lewis acid. The reaction is typically carried out at a temperature of 25°C to about 120°C for a period of about 1 hour to 6 hours. Where X is represented by OH, the reaction is typically carried out in the presence of a proton acid such as polyphosphoric acid or sulfuric acid.

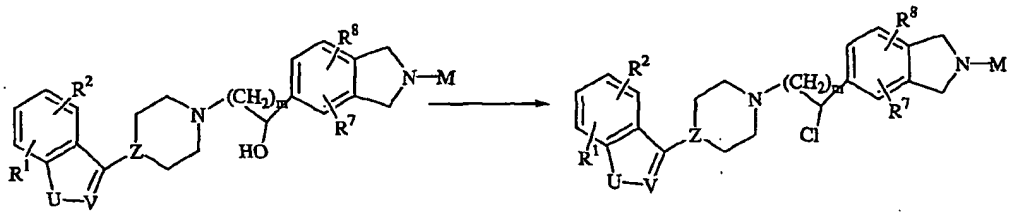
SCHEME C-3



The above scheme illustrates a method for preparing compounds of formula **13**, by reacting a compound of the formula **12** with a compound of formula 5·HCL. The reaction is typically run in the presence of a base such as potassium carbonate, sodium carbonate, triethylamine, or diisopropylethylamine. The solvent used may be water, acetonitrile, dioxane, benzene, toluene, tetrahydrofuran, methyl isobutyl ketone, or a combination of two of the formerly mentioned solvents. Inorganic salts such as a sodium or potassium halide (*e.g.*, sodium iodide or potassium iodide) may

be employed as catalysts in the reaction. The temperature of the reaction may vary from ambient to reflux temperature of the solvent used, preferably from about 80°C to 120°C, for a period of about 1 hour to about 96 hours, preferably from about 12 hours to 48 hours.

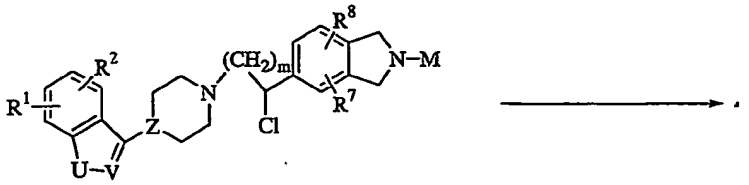
SCHEME C-4



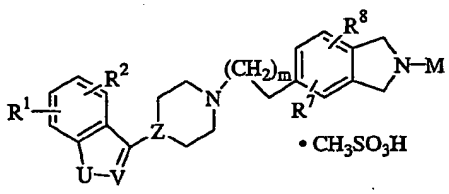
14 15

The above scheme illustrates a method for preparing compounds of the formula **15** by reacting compounds of the formula **14**. The reaction is typically run in the presence of a chlorinating reagent such as toluenesulfonyl chloride, methanesulfonyl chloride, carbon tetrachloride, or hydrogen chloride. The solvent used may be methylene chloride, dichloroethane, toluene, tetrahydrofuran, chloroform, or a combination of two of the formerly mentioned solvents. The temperature of the reaction may vary from –20°C to reflux temperature of the solvent used, preferably from about 0°C to ambient, for a period of about 1 hour to about 96 hours, preferably from about 2 hours to 12 hours.

SCHEME C-5



15



16

The above scheme illustrates a method for preparing compounds of the formula **16** by reacting compounds of the formula **15**. The reaction is typically run in the presence of a reducing reagent such as trialkyltin hydride, or triaryltin hydride. The reaction is typically run in the presence of a radical initiator such as 2,2-azobisisobutyronitrile or light. The solvent used may be benzene, toluene, tetrahydrofuran, or a combination of two of the formerly mentioned solvents. The temperature of the reaction may vary from 0°C to reflux temperature of the solvent used, preferably from about 40°C to reflux, for a period of about 1 hour to about 96 hours, preferably from about 1 hour to 4 hours.

The preparation of other compounds of the formula **1** not specifically described in the foregoing experimental section can be accomplished using combinations of the reactions described above that will be apparent to those skilled in the art.

In each of the reactions discussed or illustrated above, pressure is not critical unless otherwise indicated. Pressures from about 0.5 atmospheres to about 5 atmospheres are generally acceptable, and ambient pressure, i.e., about 1 atmosphere, is preferred as a matter of convenience.

The compounds of the formula **1**, and the intermediates shown in the above reaction schemes can be isolated and purified by conventional procedures, such as recrystallization or chromatographic separation.

The compounds of the formula 1 and their pharmaceutically acceptable salts can be administered to mammals via either the oral, parenteral (such as subcutaneous, intraveneous, intramuscular, intrasternal and infusion techniques), rectal, buccal or intranasal routes. In general, these compounds are most desirably administered in doses ranging from about 3 mg to about 600 mg per day, in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the patient being treated, the patient's individual response to said medicament, the nature and severity of the particular disorder being treated, as well as on the type of pharmaceutical formulation chosen and the overall time period and intervals over which such administration is carried out. However, a dosage level that is in the range of about 25 mg to about 100 mg per day is most desirably employed. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such higher dose levels are first divided into several small doses for administration throughout the day.

The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by any of the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the therapeutic agents of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, suppositories, jellies, gels, pastes, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the weight ratio of the compounds of this invention to the pharmaceutically acceptable carrier will be in the range from about 1:6 to about 2:1, and preferably from about 1:4 to about 1:1.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates,

together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of a compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well known to those skilled in the art.

This invention relates to methods of treating anxiety, depression, schizophrenia and the other disorders referred to in the description of the methods of the present invention, wherein a compound of this invention and one or more of the other active agents referred to above (*e.g.*, an NK1 receptor antagonist, tricyclic antidepressant, 5HT1D receptor antagonist, or serotonin reuptake inhibitor) are administered together, as part of the same pharmaceutical composition, as well as to methods in which such active agents are administered separately as part of an appropriate dose regimen designed to obtain the benefits of the combination therapy. The appropriate dose regimen, the amount of each dose of an active agent administered, and the specific intervals between doses of each active agent will depend upon the subject being treated, the specific active agent being administered and the nature and severity of the specific disorder or condition being treated. In general, the compounds of this invention, when used as a single active agent or in combination with another active agent, will be administered to an adult human in an amount from about 3 mg to about 600 mg per day, in single or divided doses, preferably from about 25 to about 100 mg

per day. Such compounds may be administered on a regimen of up to 6 times per day, preferably 1 to 4 times per day, especially 2 times per day and most especially once daily. Variations may nevertheless occur depending on the species, weight and condition of the patient being treated, the patient's individual response to said medicament, the nature and severity of the particular disorder being treated, as well as on the type of pharmaceutical formulation chosen and the overall time period and intervals over which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

A proposed daily dose of a 5HT reuptake inhibitor, preferably sertraline, in the combination methods and compositions of this invention, for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to above, is from about 0.1 mg to about 2000 mg, preferably from about 1 mg to about 200 mg of the 5HT reuptake inhibitor per unit dose, which could be administered, for example, 1 to 4 times per day. A proposed daily dose of a 5HT1D receptor antagonist in the combination methods and compositions of this invention, for oral, parenteral, rectal or buccal administration to the average adult human for the treatment of the conditions referred to above, is from about 0.01 mg to about 2000 mg, preferably from about 0.1 mg to about 200 mg of the 5HT1D receptor antagonist per unit dose, which could be administered, for example, 1 to 4 times per day.

For intranasal administration or administration by inhalation, the compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active compound. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base

such as lactose or starch. Formulations of the active compounds of this invention for treatment of the conditions referred to above in the average adult human are preferably prepared so that each metered dose or "puff" of aerosol contains 20 μg to 1000 μg of active compound. The overall daily dose with an aerosol will be within the range 100 μg to 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time.

The ability of the compounds of this invention to bind to the dopamine D2 and serotonin 2A (5HT2A) receptors can be determined using conventional radioligand receptor binding assays. All receptors can be heterologously expressed in cell lines and experiments conducted in membrane preparations from the cell lines using procedures outlined below. IC_{50} concentrations can be determined by nonlinear regression of concentration-dependent reduction in specific binding. The Cheng-Prussoff equation can be used to convert the IC_{50} to Ki concentrations.

Dopamine D2 Receptor Binding:

[^{3}H]Spiperone binding to a membrane preparation from CHO-hD2L cells is carried out in 250 μl of 50 mM Tris-HCl buffer containing 100 mM NaCl, 1 mM $MgCl_2$ and 1% DMSO at pH 7.4. Duplicate samples containing (in order of addition) the test compounds, 0.4 nM [^{3}H]spiperone and approximately 12 μg protein are incubated for 120 minutes at rt. Bound radioligand is separated by rapid filtration under reduced pressure through Whatman GF/B glass fiber filters previously treated with 0.3% polyethyleneimine. Radioactivity retained on the filter is determined by liquid scintillation spectrophotometry.

Certain of the title compounds of Examples 1–164 were tested using the above assay, in which specific binding determined in the presence of 1 mM haloperidol was 95%. The results of the testing are shown in Table A below.

Serotonin 2A Binding:

[^{3}H] Ketanserin binding to Swiss-h5HT2A cell membranes can be carried out in 250 μl of 50 mM Tris-HCl buffer pH 7.4. Duplicate samples containing (in order of addition) test compounds, 1.0 nM [^{3}H]ketanserin, and approximately 75 μg protein are incubated for 120 minutes at rt. Bound radioligand is separated by rapid filtration under reduced pressure through Whatman GF/B glass fiber filters previously treated

with 0.3% polyethyleneimine. Radioactivity retained on the filter is determined by liquid scintillation spectrophotometry.

Certain of the compounds of Examples 1–164 were tested using the above assay, in which specific binding determined in the presence of 1 mM ketanserin was 90%. The results of the testing are shown in Table A below.

TABLE A

Example	Compound Name	D2 K1	5HT2A K1
1	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-methanone	95.70	
2	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(3-methoxy-phenyl)-ethanone	103.87	
3	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-thiophen-2-yl-ethanone	92.41	
4	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-phenoxy-propan-1-one		
5	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(2,5-dimethyl-2H-pyrazol-3-yl)-methanone	54.80	
6	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(2,5-dimethyl-2H-pyrazol-3-yl)-methanone	65.00	
7	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	55.10	
8	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-m-tolyl-methanone		
9	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(4-chloro-phenoxy)-ethanone		
10	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-3-phenyl-propan-1-one		
11	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(3,4-dimethoxy-phenyl)-ethanone		
12	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(4-chloro-phenyl)-ethanone		
13	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(4-methoxy-phenyl)-methanone	45.00	
14	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-phenyl-ethanone	68.83	

Example	Compound Name	D2 K1	5HT2A K1
15	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(2,5-dimethoxy-phenyl)-ethanone		
16	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indole-1-carboxylic acid phenyl ester		
17	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-furan-2-yl-methanone	52.00	1.10
18	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one		
19	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-cyclopentyl-methanone		
20	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-benzyloxy-ethanone		
21	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-phenyl-methanone	83.00	
22	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-cyclopentyl-ethanone		
23	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone	16.73	0.11
25	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-ethanone	13.42	0.55
26	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-cyclopropyl-methanone	66.45	1.10
27	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone		
27	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-propan-1-one	59.04	2.15
28	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indole-1-carboxylic acid isopropylamide	29.39	0.30
28	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-2,2-dimethyl-propan-1-one	106.00	0.90
29	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-pentan-1-one	64.31	1.85
30	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-3-methyl-butan-1-one		1.40
31	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-2-methyl-propan-1-one	29.80	0.80
32	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-	44.60	0.60

Example	Compound Name	D2 K1	5HT2A K1
	tetrahydro-2H-benzo[cd]indol-1-yl}-butan-1-one		
33	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-phenyl-methanone		
34	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	6.48	0.32
34	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone		
34	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone		
35	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-propan-1-one	26.38	2.00
36	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-butan-1-one	47.99	1.05
37	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	39.97	1.60
38	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-pentan-1-one	78.50	
39	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one	81.31	
40	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-cyclopentyl-methanone	68.82	
41	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-cyclohexyl-methanone		
42	3-{4-[2-(6-Chloro-1-methanesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole	15.49	1.65
43	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid methylamide	8.94	0.15
44	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid ethylamide	9.00	0.09
45	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid propylamide	16.49	3.48
46	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid isopropylamide	62.40	2.70
47	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid tert-butylamide		1.15
48	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid cyclopentylamide		2.40

Example	Compound Name	D2 K1	5HT2A K1
49	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid phenylamide		5.10
50	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	23.45	4.95
51	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone	30.94	0.65
52	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone	8.77	0.30
53	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-propan-1-one	24.37	0.70
54	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-cyclopropyl-methanone	24.00	2.20
55	1-{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-ethanone; compound with methanesulfonic acid	20.49	3.92
56	1-(7-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone; compound with methanesulfonic acid	36.37	8.77
57	1-(7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone; compound with methanesulfonic acid	38.88	0.01
60	{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-(4-fluoro-phenyl)-methanone; compound with methanesulfonic acid	59.29	5.00
61	1-{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-propan-1-one; compound with methanesulfonic acid	16.49	2.30
62	1-(6-{2-[4-(1H-Indazol-3-yl)-piperazin-1-yl]-ethyl}-3,3-dimethyl-3,4-dihydro-2H-quinolin-1-yl)-ethanone	8.08	1.30
63	1-{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone; compound with methanesulfonic acid	19.97	1.35
64	1-{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-2-methyl-propan-1-one; compound with methanesulfonic acid	25.98	1.70
65	1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-ethanone; compound with	5.43	0.55

Example	Compound Name	D2.K1	5HT2A K1
	methanesulfonic acid		
66	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone	7.42	1.20
73	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydro-isoindol-2-yl}-ethanone; compound with methanesulfonic acid	23.16	0.42
74	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydro-isoindol-2-yl}-ethanone; compound with methanesulfonic acid		1.83
81	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydro-isoindol-2-yl}-2-morpholin-4-yl-ethanone	77.00	1.35
83	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-ethanone	70.94	3.10
85	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-dimethylamino-ethanone	49.70	4.20
86	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-piperidin-1-yl-ethanone		2.40
87	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-morpholin-4-yl-ethanone	56.48	2.90
88	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-[(2-dimethylamino-ethyl)-methyl-amino]-ethanone	55.50	4.67
89	1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-diethylamino-ethanone	67.45	9.79
91	5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindole-2-carboxylic acid (4-fluoro-phenyl)-amide	65.19	1.25
95	{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-phenyl-methanone		2.55
96	1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone	18.97	0.85
97	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-methanone	51.61	
97	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-methanone		
98	{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-methanone	57.92	4.35
98	{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2H-quinolin-1-yl}-(4-fluoro-phenyl)-methanone		
99	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-fluoro-2,3-dihydro-indol-1-yl}-ethanone	80.11	1.32

Example	Compound Name	D2 K1	5HT2A K1
100	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-fluoro-2,3-dihydro-indol-1-yl}-ethanone	20.00	0.34
101	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone	20.45	0.64
102	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone	16.83	0.12
103	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone	56.44	1.46
104	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone	13.96	0.50
105	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone	50.48	3.38
106	1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	2.71	0.30
107	1-(6-Chloro-5-{2-[4-(5-methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		24.50
108	1-(6-Chloro-5-{2-[4-(7-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		8.05
109	1-(6-Chloro-5-{2-[4-(7-methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		20.50
110	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperidin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	2.45	0.45
111	1-(6-Chloro-5-{2-[4-(5-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	83.67	21.00
112	1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	13.98	2.15
113	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	12.63	0.55
114	1-(6-Chloro-5-{2-[4-(5-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		23.00
115	1-(6-Chloro-5-{2-[4-(5-chloro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		26.00
116	1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	18.98	2.65
117	1-(6-Chloro-5-{2-[4-(6-methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	20.93	6.90
118	1-(6-Chloro-5-{2-[4-(7-methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-		19.50

Example	Compound Name	D2 K1	5HT2A K1
	ethyl}-2,3-dihydro-indol-1-yl)-ethanone		
119	1-{5-[2-(4-Benzo[b]thiophen-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	48.76	14.00
120	1-(6-Chloro-5-{2-[4-(1H-indazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	9.95	1.55
121	1-(5-{2-[4-(6-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	10.39	0.10
122	1-(5-{2-[4-(5-Methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	62.63	8.05
123	1-(5-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	93.00	1.85
124	1-(5-{2-[4-(7-Methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		30.50
125	1-(5-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	67.35	2.20
126	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone	88.00	1.15
127	1-(5-{2-[4-(5-Fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		18.50
128	1-(5-{2-[4-(5-Chloro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	78.00	5.85
129	1-(5-{2-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		1.50
130	1-(5-{2-[4-(7-Methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone		14.35
131	1-{5-[2-(4-Benzo[b]thiophen-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone	20.35	2.20
132	1-(5-{2-[4-(1H-Indazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	62.16	1.30
134	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone	21.35	0.60
135	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-propan-1-one	12.41	0.90
136	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-Indol-1-yl}-butan-1-one	29.98	1.50
137	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	36.66	0.07

Example	Compound Name	D2 K1	5HT2A K1
138	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclopropyl-methanone	15.97	0.65
139	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-pentan-1-one	55.23	0.20
140	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one	53.96	0.35
141	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2,2-dimethyl-propan-1-one	22.49	0.20
142	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclopentyl-methanone	36.00	0.40
143	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclohexyl-methanone	75.94	0.45
144	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-phenyl-methanone	34.99	0.55
145	3-{4-[2-(1-Methanesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole	12.49	0.06
146	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid methylamide	60.50	0.15
147	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid ethylamide	74.00	0.35
148	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid propylamide	56.00	0.35
149	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid isopropylamide		0.20
150	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid tert-butylamide		0.30
151	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid cyclopentylamide	69.00	0.55
152	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid phenylamide		2.75
154	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-pyrrolidin-1-yl-ethanone	10.39	1.35
155	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-diethylamino-ethanone	35.33	1.85
156	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-dimethylamino-ethanone	24.90	2.08
157	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-	77.48	1.14

Example	Compound Name	D2 K1	5HT2A K1
	indol-1-yl}-2-morpholin-4-yl-ethanone		
158	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-piperidin-1-yl-ethanone	23.54	2.48
160	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-pyrrolidin-1-yl-propan-1-one	18.57	0.65
161	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-diethylamino-propan-1-one	18.57	0.75
162	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-dimethylamino-propan-1-one	12.40	2.08
163	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-morpholin-4-yl-propan-1-one	27.71	2.77
164	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-piperidin-1-yl-propan-1-one	20.90	2.13

The following Examples illustrate the preparation of the compounds of the present invention. Melting points are uncorrected. NMR data are reported in parts per million and are referenced to the deuterium lock signal from the sample solvent.

EXAMPLES

PREPARATION 1

5-(2-Chloroacetyl)-3,3-dimethyl-1,3-dihydroindol-2-one

A 12.5 L 4-neck flask equipped with a mechanical stirrer, reflux condenser and two stoppers and heating mantle, was charged with $AlCl_3$ (633.29 g, 4.75 mol), 2 L of carbon disulfide and chloroacetyl chloride (87 mL, 1.09 mol) and this was stirred at room temperature (rt) during the portionwise addition of 3,3-dimethyl-1,3-dihydro-indol-2-one (123.5 g, 0.766 mol). This mixture was then heated to reflux for 3 hours, then cooled overnight. The solvent was decanted and the reaction was quenched with addition of ice and water (8 L). The suspension was stirred vigorously for 1.5 hours, followed by filtration. The solids were washed with water (4.2 L) and then dried overnight in a vacuum oven at 50 degrees Celsius (°C) (192.19 g of 5-(2-chloroacetyl)-3,3-dimethyl-1,3-dihydroindol-2-one). 29.54 g of this material was taken up in hot acetone and purified by flash chromatography (250 g silica gel)

eluting with acetone which provided >96% pure 5-(2-chloroacetyl)-3,3-dimethyl-1,3-dihydroindol-2-one by HPLC. Yield = 15.54 g (52%); MS (APCI), $(M + 1)^+ = 238$. Anal. calculated for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.09; N, 5.89. Found: C, 61.04; H, 5.15; N, 5.38%.

PREPARATION 2

5-(2-Chloroethyl)-3,3-dimethyl-1,3-dihydroindol-2-one

A 5 L 4-neck flask equipped with a mechanical stirrer, 1 L addition funnel and two stoppers were charged with 5-(2-chloroacetyl)-3,3-dimethyl-1,3-dihydroindol-2-one (162.65 g, 0.684 mol) and this was taken up in trifluoroacetic acid (700 mL). The solution was cooled in an ice/water bath, followed by addition of triethylsilane (260 mL) over a 1 hour period. The reaction was stirred at rt ovemight. The mixture as poured into a 12.5 L flask containing 8 L of rapidly stirring water. The reaction flask was washed with 1.5 L of water and 2 L of heptanes, both added to the 12.5 L flask. The mixture was again stirred overnight. The suspension was vacuum filtered and the solids were washed with water (2 L) and heptanes (2 L) and dried overnight in a vacuum oven (73.2 g). The solid was purified by flash chromatography (550 g silica gel) eluting with acetone (2 L). Yield = 68.38g (45%); MS (APCI), $(M + 1)^+ = 224$. Anal. calculated for $C_{12}H_{12}ClNO_2$: C, 64.43; H, 6.31; N, 6.29. Found: C, 64.35; H, 6.36; N: 5.84.

PREPARATION 3

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-1,3-dihydro-indol-2-one

A 500 mL round bottom (RB) flask was charged with 3-piperazin-1-yl-benzo[d]isothiazole (12.5 g, 5.0 mol), 5-(2-chloroethyl)-3,3-dimethyl-1,3-dihydroindol-2-one (11.5 g, 5.0 mol) and sodium carbonate (10.5 g, 10.0 mol), diluting with water (200 mL). The stirring reaction was warmed to reflux for 24 hours. The reaction was slowly cooled with vigorous stirring and a solid formed. The tan solid was filtered washed with ether and dried in a vacuum oven. Yield = 19.49 g (96%); 1H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (s, 6 H) 2.61 (m, 8 H) 3.42 (m, 5 H) 6.73 (d, J=7.82 Hz,

1 H) 7.00 (dd, J=7.82 Hz, 1 H) 7.14 (d, 1 H) 7.41 (t, J=7.69 Hz, 1 H) 7.53 (t, J=7.45 Hz, 1 H) 8.03 (d, J=9.04 Hz, 2 H) 10.21 (s, 2 H)

PREPARATION 4

3-{4-[2-(3,3-Dimethyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole

A solution of 5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-1,3-dihydro-indol-2-one (810 mg, 2.0 mmol) in toluene (15 mL) with stirring at rt was treated with borane dimethyl sulfide in toluene (2 mL, 4 mmol). The reaction was warmed to reflux for 1 hour. The reaction was cooled and treated with a 10% aqueous solution of sodium carbonate (10 mL) and warmed to reflux for 20 hours. The reaction was cooled and the layers were separated. The aqueous layers were extracted with ethyl acetate (2 x 20 mL). The combined organics were dried over magnesium sulfate, filtered and the filtrate concentrated. The crude product was eluted through a flash column (silica gel 40, 230-400 mesh, methylene chloride (CH_2Cl_2) to 8% ethanol (EtOH) and 1% ammonium hydroxide (NH_4OH in CH_2Cl_2) to give the title compound as a brown oily solid, yield = 620 mg (79%). ^{1}H-NMR ($CDCl_3$, δ): 7.91 (d, J=8.30 Hz, 1 H) 7.81 (d, J=8.30 Hz, 1 H) 7.47 (t, J=7.56 Hz, 1 H) 7.35 (t, J=7.56 Hz, 1 H) 6.89 (m, 2 H) 6.59 (d, J=8.30 Hz, 1 H) 3.61 (m, 4 H) 3.30 (s, 2 H) 2.69 (m, 8 H) 1.30 (s, 6 H).

EXAMPLE 1

{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-methanone

3-{4-[2-(3,3-Dimethyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-1,2-benzo[d]isothiazole was diluted to 0.20 M with anhydrous dichloromethane, then delivered to an 8 mL vial via pipette (0.20 mmol). To the amine solution was added polystyrene-N-Methylmorpholine resin (PS-N-Methylmorpholine resin) (0.40 mmol). Isoxazole-4-fluoro-benzoyl chloride (0.40 mmol) was diluted to 0.20 M with dichloromethane, and added at rt. The solution was shaken overnight at rt. Polyamine scavenging resin (0.5 mmol) was added. The solution was shaken overnight at rt, then filtered into an 8 mL vial. The filtrate was evaluated by MS, then

concentrated via HT-12 GeneVac. Crude was purified by HPLC (30x100 mm ODS-A C(18) 5u column). 4-[2{5-[2-(4-1,2-Benzisothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(4-fluoro-phenyl)-methanone was isolated in 98% purity @ 254 nm, LCMS (APCI) 515 $[M+H]^+$.

The amides of Examples 2-22 were synthesized in combinatorial library format following the steps outlined in Example 1 on a 0.2 mmol scale using 3-{4-[2-(3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-1,2-benz[o]isothiazole with appropriate acid chloride starting materials and PS-*N*-methylmorpholine. The crude products were purified by HPLC (30x100 mm ODS-A C(18) 5u column).

EXAMPLE	COMPOUND NAME	DATA
#2	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(3-methoxy-phenyl)-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 541 $[M+H]^+$
#3	1-{5-[2-(4-Benzo[d]isothiazol-3-yl piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3 dihydro-indol-1-yl}-2-thiophen-2-yl ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 517 $[M+H]^+$
#4	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-phenoxy-propan-1-one	Isolated in 96% purity @ 254 nm; LCMS (APCI) 541 $[M+H]^+$
#5	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(2,5-dimethyl-2H-pyrazol-3-yl)-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 515$[M+H]^+$
#6	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-butan-1-one	Isolated in 100% purity @ 254 nm; LCMS (APCI) 463 $[M+H]^+$
#7	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	Isolated in 100% purity @ 254 nm; LCMS (APCI) 463 $[M+H]^+$

EXAMPLE	COMPOUND NAME	DATA
#8	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-m-tolyl-methanone	Isolated in 98% purity @ 254 nm; LCMS (APCI) 511 $[M+H]^+$
#9	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(4-chloro-phenoxy)-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 562 $[M+H]^+$
#10	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-3-phenyl-propan-1-one	Isolated in 97% purity @ 254 nm; LCMS (APCI) 525 $[M+H]^+$
#11	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(3,4-dimethoxy-phenyl)-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 571 $[M+H]^+$
#12	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(4-chloro-phenyl)-ethanone	Isolated in 96% purity @ 254 nm; LCMS (APCI) 546 $[M+H]^+$
#13	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-(4-methoxy-phenyl)-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 527 $[M+H]^+$
#14	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-phenyl-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 511 $[M+H]^+$
#15	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-(2,5-dimethoxy-phenyl)-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 571 $[M+H]^+$
#16	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indole-1-	Isolated in 90% purity @ 254 nm; LCMS (APCI) 513 $[M+H]^+$

EXAMPLE	COMPOUND NAME	DATA
	carboxylic acid phenyl ester	
#17	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-furan-2-yl-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 487 $[M+H]^+$
#18	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one	Isolated in 100% purity @ 254 nm; LCMS (APCI) 477 $[M+H]^+$
#19	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-cyclopentyl-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 489 $[M+H]^+$
#20	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-benzyloxy-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 541 $[M+H]^+$
#21	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-phenyl-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 497 $[M+H]^+$
#22	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-2-cyclopentyl-ethanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 503 $[M+H]^+$

EXAMPLE 23

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone

3-{4-[2-(3,3-Dimethyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-1,2-benz[o]isothiazole (0.81 mmol, 313 mg) was diluted with anhydrous THF (5 mL) and triethylamine (0.225 mL) then treated with acetyl chloride (0.711 ml) and allowed to stir for 72 hours (h or hr). The reaction was filtered and the filtrate was concentrated. The crude solid was washed with saturated sodium carbonate solution (10 mL) and extracted with methylene chloride (25 mL) dried and concentrated to oily solid. The solid was crystallized from ether to yield pure 1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone : Yield: 182 mg

(52%). ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 1.34 (s, 6 H) 2.19 (s, 3 H) 2.76 (m, 8 H) 3.60 (s, 4 H) 3.75 (s, 2 H) 6.98 (s, 1 H) 7.05 (d, *J*=8.06 Hz, 1 H) 7.34 (t, *J*=7.57 Hz, 1 H) 7.46 (t, *J*=7.57 Hz, 1 H) 7.80 (d, *J*=8.30 Hz, 1 H) 7.90 (d, *J*=8.30 Hz, 1 H) 8.08 (d, *J*=8.06 Hz, 1 H) MS (APCI) = 435.2 $[M+H]^+$.

EXAMPLE 24

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indole-1-carboxylic acid isopropylamide

A solution of 3-{4-[2-(3,3-dimethyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-1,2-benz[o]isothiazole (0.4 mmols, 160 mg) in THF (5mL) was treated by dropwise addition with isopropyl isocyanate at rt (RT or rt) and allowed to stir for 4 days. The reaction was concentrated to dryness, diluted with H_2O and extracted with CH_2Cl_2. The organics were placed through a phase separator and dried down in a 100X16mm tube, resulting in a solid. The solid was then recrystallized from acetonitrile to yield pure 5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,3-dimethyl-2,3-dihydro-indole-1-carboxylic acid isopropylamide. Yield: 112 mg (58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.07 (d, *J*=6.59 Hz, 6 H) 1.22 (s, 6 H) 2.60 (m, 8 H) 3.40 (s, 4 H) 3.57 (s, 2 H) 3.80 (m, 1 H) 6.14 (d, *J*=7.81 Hz, 1 H) 6.90 (d, *J*=8.05 Hz, 1 H) 6.98 (s, 1 H) 7.38 (t, *J*=7.69 Hz, 1 H) 7.51 (t, *J*=7.81 Hz, 1 H) 7.65 (d, *J*=8.05 Hz, 1 H) 8.00 (d, *J*=8.78 Hz, 2 H).

PREPARATION 5

6-(2-Chloro-acetyl)-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one

A RB flask was charged with 60 mL dichloroethane and $AlCl_3$ (11.5 g, 86 mmol, 3 eq) and cooled on an ice-bath. To this solution was added, portionwise, 5.0 g (29 mmol, 1 eq) of the known 2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one (Protiva, M.; Sedivy, Z.; Holubek, J.; Svatek, E.; Nemec, J. *Collection of Czechoslovak Chemical Communications* **1985**, *50*, 1888-98, Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871-8). After 20 min, 2.8 mL (34 mmol, 1.2 eq) of chloroacetylchloride was added and the solution was allowed to warm slowly to rt. After 30 hours at rt the solution was poured carefully into 500 mL of iced-water and the resulting precipitate

was filtered and washed with chloroform. The white solid was oven dried overnight at 60 °C under vacuum to give 6.0 g (83 % yield) of the desired product as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (m, J=12.3, 12.3, 12.1, 3.3 Hz, 1 H) 1.7 (m, 1 H) 2.0 (m, J=10.4, 7.2, 3.7, 1.7 Hz, 1 H) 2.1 (ddd, J=12.0, 8.7, 3.4 Hz, 1 H) 2.7 (m, 1 H) 3.1 (dd, J=19.0, 7.1 Hz, 1 H) 3.3 (s, 1 H) 3.4 (dd, J=12.1, 5.2 Hz, 1 H) 5.0 (m, 2 H) 6.7 (d, J=8.3 Hz, 1 H) 7.8 (dd, J=8.3, 1.0 Hz, 1 H) 10.6 (s, 1 H). MS (APCI), $(M+1)^+$ = 250.

PREPARATION 6

6-(2-Chloro-ethyl)-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one

A RB flask was charged with 5.85 g (23 mmol, 1 eq) 6-(2-chloro-acetyl)-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one, 18 mL (10 eq) trifluoroacetic acid and 11 mL (3 eq) triethylsilane and heated to 60 °C for 4 hr. The reaction mixture was then quenched carefully into 300 mL of iced water and extracted with 400 mL of CH_2Cl_2. The aqueous layer was extracted with an additional 200 mL CH_2Cl_2, dried over $MgSO_4$ and concentrated in vacuo to give 11 g of a semi-solid. This material was triturated with 200 mL of 1:1 diethylether:hexanes and the resulting solid dried *in vacuo* to give 4.68 g (86 % yield) of the desired material as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.1 (m, 1 H) 1.8 (m, 1 H) 2.0 (m, 1 H) 2.1 (m, 1 H) 2.5 (m, 1 H) 2.7 (dd, J=17.6, 7.3 Hz, 1 H) 2.9 (td, J=14.8, 6.6 Hz, 2 H) 3.3 (m, 1 H) 3.7 (m, 2 H) 6.5 (d, J=7.6 Hz, 1 H) 6.9 (d, J=7.8 Hz, 1 H) 10.1 (s, 1 H). MS (APCI), $(M+1)^+$ = 236.

PREPARATION 7

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one

A 20 mL reaction vial was charged with 0.47 g (2 mmol, 1 eq) 6-(2-chloro-ethyl)-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one, 0.51 g 3-piperazin-1-yl-benzo[d]-iso-thiazole hydrochloride, and 5 mL of 1 M aqueous sodium carbonate (Na_2CO_3) and heated to 100°C for 60 h. The solid was filtered, washed with water and dried *in vacuo* overnight. The resulting solid was purified by medium pressure liquid chromatography (MPLC) (ethyl acetate (EtOAc) eluent) to give 0.36 g (43 % yield) of

the desired material as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.3 (qd, *J*=12.3, 3.5 Hz, 1 H) 1.9 (m, 1 H) 2.2 (m, 1 H) 2.4 (dt, *J*=12.2, 4.4 Hz, 1 H) 2.6 (m, 3 H) 2.8 (m, 6 H) 3.3 (dd, *J*=11.8, 5.0 Hz, 1 H) 3.6 (s, 4 H) 6.6 (d, *J*=7.6 Hz, 1 H) 7.0 (d, *J*=7.8 Hz, 1 H) 7.3 (m, 1 H) 7.5 (m, 1 H) 7.8 (d, *J*=8.1 Hz, 1 H) 7.9 (d, *J*=8.1 Hz, 1 H) 8.2 (s, 1 H). MS (APCI), $(M+1)^+$ = 292, 419.

PREPARATION 8

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,2,2a,3,4,5-hexahydro-benzo[cd]indole

A RB flask was charged with 5.0 g (12 mmol, 1 eq) 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-1H-benzo[cd]indol-2-one and 50 mL tetrahydrofuran (THF) and cooled on an ice bath. The reaction was treated dropwise with 48 mL (48 mmol, 4 eq) 1 M borane-THF (BH_3-THF) in THF over 0.5 h and then allowed to warm slowly to rt. After 24 h the reaction was quenched with 20 mL methanol (MeOH) (gas evolution) and heated at 50°C for 15 h. The reaction was cooled, partitioned between CH_2Cl_2 and brine. The organic extracts were dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated to give 4.7 g of a yellow foam that was a mixture of indole and indoline products by ^{1}H NMR. This mixture was taken on without purification.

A RB flask was charged with 4.38 g of the above mixture and 43 mL acetic acid (HOAc). This mixture was treated with 1.8 g (27 mmol, 2.5 eq) sodium cyanoborohydride ($NaCNBH_3$) and stirred at rt for 15 h. The reaction solvent was removed *in vacuo* and the resulting solid was dissolved in 200 mL CH_2Cl_2 and washed with 1 M sodium bicarbonate ($NaHCO_3$). The aqueous layer was back-extracted with 100 mL CH_2Cl_2. The combined organic layers were washed with brine, separated, and dried over $MgSO_4$. Concentration *in vacuo* gave 4.0 g of a yellow foam that was purified by MPLC to give 1.65 g (33 % yield) of the desired material as a slightly yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.3 (d, *J*=10.5 Hz, 1 H) 1.7 (s, 1 H) 2.1 (m, 2 H) 2.6 (dd, *J*=10.3, 5.4 Hz, 4 H) 2.8 (m, 7 H) 3.1 (m, 2 H) 3.6 (m, 5 H) 6.5 (d, *J*=7.6 Hz, 1 H) 6.8 (d, *J*=7.6 Hz, 1 H) 7.3 (dd, *J*=8.1, 7.1 Hz, 1 H) 7.5 (m, 1 H) 7.8 (m, 1 H) 7.9 (d, *J*=8.3 Hz, 1 H). MS (APCI), $(M+1)^+$ = 403.

EXAMPLE 25

1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-ethanone

A solution of 1.0 g (2.0 mmol, 1 eq) 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,2,2a,3,4,5-hexahydro-benzo[cd]indole was treated with 0.689 mL (4.9 mmol, 2 eq) triethylamine (Et_3N) and then 0.263 mL (3.7 mmol, 1.5 eq) acetyl chloride and stirred at rt for 20 h. The reaction was quenched with 1 M $NaHCO_3$, filtered through 5 μm PTFE (phase-separating filter), and concentrated *in vacuo* to give 1.19 g (quantitative yield) of a pale-yellow foam. ^1H NMR (400 MHz, $CDCl_3$) (Integration does not take into account a 3:1 mixture of rotamers, the presence of which is most pronounced at the peaks labeled major/minor.) ppm 1.1 (m, 3 H) 1.2 (m, 1 H) 1.3 (m, 1 H) 1.8 (m, 1 H) 2.1 (m, 5 H) 2.4 (s, 1 H) 2.6 (m, 5 H) 2.8 (m, 7 H) 2.9 (t, *J*=7.3 Hz, 1 H) 3.3 (m, 1 H) 3.5 (dd, *J*=11.2 Hz, 1 H) 3.6 (m, 4 H) 4.2 (major, t, *J*=9.2 Hz, 1 H) 4.6 (minor, 1 H) 6.8 (minor, d, *J*=8.1 Hz, 1 H) 7.0 (major, m, 1 H) 7.3 (m, 1 H) 7.4 (t, *J*=7.6 Hz, 1 H) 7.8 (d, *J*=8.1 Hz, 2 H) 7.9 (d, *J*=8.1 Hz, 1 H). MS (APCI), $(M+1)^+ = 447$.

The title compounds of Examples 26 through 33 were prepared from 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,2,2a,3,4,5-hexahydro-benzo[cd]indole in a fashion similar to that reported above. R_t (min) reported is for the following high pressure liquid chromatography (HPLC) conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Purity for each compound reported is > 90% by UV (254 nM).

EXAMPLE	COMPOUND NAME	DATA
#26	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-cyclopropyl-methanone	HPLC: $R_t = 3.005$; MS (APCI), $(M+1)^+ = 473$
#27	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-propan-1-one	HPLC: $R_t = 2.898$; MS (APCI), $(M+1)^+ = 461$

#28	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-2,2-dimethyl-propan-1-one	HPLC: R_t = 3.885; MS (APCI), $(M+1)^+$ = 489
#29	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-pentan-1-one	HPLC: R_t = 3.935; MS (APCI), $(M+1)^+$ = 489
#30	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-3-methyl-butan-1-one	HPLC: R_t = 3.753; MS (APCI), $(M+1)^+$ = 489
#31	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-2-methyl-propan-1-one	HPLC: R_t = 3.218; MS (APCI), $(M+1)^+$ = 475
#32	1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-butan-1-one	HPLC: R_t = 3.302; MS (APCI), $(M+1)^+$ = 475
#33	{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2a,3,4,5-tetrahydro-2H-benzo[cd]indol-1-yl}-phenyl-methanone	HPLC: R_t = 3.441; MS (APCI), $(M+1)^+$ = 509

PREPARATION 9

3-{4-[2-(6-Chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole

A solution of borane dimethyl sulfide in THF (9.6 mL, 19.2 mmol) was added dropwise to a suspension of 3.17g (7.7 mmols) of known 5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-1,3-dihydro-indol-2-one (Howard, Harry R.; Lowe, John A. III; Seeger, Thomas F.; Seymour, Patricia A.; Zorn, Stevin H.; Maloney, Patrick R.; Ewing, Frank E.; Newman, Michael E.; Schmidt, Anne W.; et al., "3-Benzisothiazolylpiperazine Derivatives as Potential Atypical Antipsychotic Agents",

Journal of Medicinal Chemistry **1996**, *39(1)*, 143-8) in THF (15 mL), with stirring at 0°C. The reaction was warmed to reflux for 2 hours. The reaction was cooled and treated with a 30% aqueous solution of sodium carbonate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organics were dried over magnesium, filtered and the filtrate concentrated. The crude product was eluted through a flash column (silica gel 40, 230-400 mesh, CH_2Cl_2 to 8% EtOH and 1% NH_4OH in CH_2Cl_2) to give the title compound as a solid, yield = 348 mg (11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.01 (m, 2 H) 3.16 (m, 2 H) 3.31 (m, 4 H) 3.51 (m, 4 H) 3.67 (d, *J*=11.72 Hz, 2 H) 4.07 (d, *J*=13.68 Hz, 2 H) 7.04 (s, 1 H) 7.28 (s, 1 H) 7.45 (t, *J*=8.30 Hz, 1 H) 7.56 (t, *J*=8.06 Hz, 1 H) 8.10 (m, 2 H) 11.32 (s, 1 H): MS (APCI), $(M+1)^+$ = 399.0.

EXAMPLE 34

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone

A solution of 3-{4-[2-(6-chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (500 mg, 1.25 mmols) in THF (10 mL) with triethylamine (0.262 mL, 1.88 mmols) was treated with acetyl chloride 0.088 mL, 1.25 mmols) and stirred for 16 hours at rt. The reaction was quenched with water, extracted with methylene chloride and filtered through 5 µm PTFE (phase-separating filter), and concentrated *in vacuo*, followed by a crystallization from isopropyl alcohol to yield : 510 mg (93%) of 1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 (m, 2 H) 3.07 (m, 2 H) 3.23 (m, 1 H) 3.49 (t, *J*=8.43 Hz, 1 H) 3.84 (m, 2 H) 4.49 (t, *J*=8.55 Hz, 1 H) 7.64 (s, 1 H) 7.81 (m, 1 H) 7.94 (m, 1 H) 8.43 (m, 1 H); mp = 160.2-162.3 °C: MS (APCI), $(M+1)^+$ = 441.1.

EXAMPLE 35

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-propan-1-one

A solution of 3-{4-[2-(6-chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (375 mg, 0.94 mmols) in THF (2.0mL) with triethylamine (0.196

mL, 1.41 mmols) was treated with propionyl chloride (0.083 mL, 0.95 mmols) and stirred for 16 hours at rt. The reaction was quenched with sodium hydroxide (1N, 5 mL), extracted with methylene chloride and filtered through 5 µm PTFE (phase-separating filter), and concentrated *in vacuo*, followed by a crystallization from isopropyl alcohol to yield: 207 mg (48%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 455.2 $[M+H]^+$.

The title compounds of Examples 36 through 42 were prepared from 3-{4-[2-(6-chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole in a fashion similar to that reported above using the appropriate commercially available acid chloride.

EXAMPLE	ACID CHLORIDE	COMPOUND NAME	DATA
#36	butyryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-butan-1-one	Yield: 265 mg (60%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 469.2 $[M+H]^+$.
#37	isobutyryl chloride	1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	Yield: 136 mg (31%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 469.3 $[M+H]^+$.
#38	valeryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-pentan-1-one	Yield: 310 mg (67%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 483.3 $[M+H]^+$.
#39	isovaleryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one	Yield: 198 mg (44%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 483.2 $[M+H]^+$.

#40	cyclopentane carbonyl chloride	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-cyclopentyl methanone	Yield: 332 mg (72%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 495.2 $[M+H]^+$.
#41	cyclohexane carbonyl chloride	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-cyclohexyl- methanone	Yield: 166 mg (35%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 509.3 $[M+H]^+$.
#42	methane sulfonyl chloride	3-{4-[2-(6-Chloro-1-methanesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole	Yield: 83 mg (18%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 477.2 $[M+H]^+$.

EXAMPLE 43

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-Indole-1-carboxylic acid methylamide

A solution of the product of Preparation 9, 3-{4-[2-(6-chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (160 mg, 0.4 mmols in THF (5mL) was treated by dropwise addition with above methyl isocyanate at rt and allowed to stir for 72 hours. The reaction was concentrated to dryness, diluted with H_2O and extracted with methylene chloride and filtered through 5 μm PTFE (phase-separating filter), and concentrated *in vacuo*, followed by a crystallization from acetonitrile to yield: 164 mg (90%). R_t (min) reported is for the following HPLC conditions: 65:35 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: $R_t = 4.856$; MS (APCI), $(M+1)^+ = 456.1$

The title compounds of Examples 44-49 were prepared from 3-{4-[2-(6-chloro-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole in a fashion similar to that reported above using the appropriate commercially available isocyanate.

EXAMPLE	ISOCYANATE	COMPOUND NAME	DATA
#44	ethyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid ethylamide	Yield: 170 mg (90%) Isolated in 100% purity @ 254 nm HPLC: R_t = 6.216; MS (APCI), $(M+1)^+$ = 470.1.
#45	n-propyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid propylamide	Yield: 178 mg (92%) Isolated in 100% purity @ 254 nm HPLC: R_t = 8.880; MS (APCI), $(M+1)^+$ = 484.1.
#46	isopropyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid isopropylamide	Yield: 100 mg (52%) Isolated in 100% purity @ 254 nm HPLC: R_t = 8.862; MS (APCI), $(M+1)^+$ = 484.1.
#47	t-butyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid tert-butylamide	Yield: 94 mg (47%) Isolated in 100% purity @ 254 nm HPLC: R_t = 17.330; MS (APCI), $(M+1)^+$ = 498.2.
#48	cyclopentyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid cyclopentylamide	Yield: 200 mg (98%) Isolated in 100% purity @ 254 nm HPLC: R_t = 15.499; MS (APCI), $(M+1)^+$ = 510.1.
#49	phenyl	5-[2-(4-	Yield: 120 mg (58%)

	isocyanate	Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indole-1-carboxylic acid phenylamide	Isolated in 100% purity @ 254 nm HPLC: R_t = 13.190; MS (APCI), $(M+1)^+$ = 518.1.

PREPARATION 10

6-Chloro-5-(3-chloro-propionyl)-1,3-dihydro-indol-2-one

A 500mL RB flask equipped with a stirrer, reflux condenser and heating mantle, was charged with aluminum chloride ($AlCl_3$) (14.76 g, 0.11 mol), 75 mL of carbon disulfide and 3-chloropropionyl chloride (2.21 mL, 0.023 mol) and this was stirred at rt during the portionwise addition of 6-chloro oxindole (3.0 g, 0.0179 mol). This mixture was then heated to reflux for 3 hours, then cooled. The solvent was decanted and the reaction was quenched with addition of ice and water. The suspension was stirred vigorously for 0.5 hours, followed by filtration. The solids were washed with water and then dried overnight in a vacuum oven. Yield = 4.23 g (92%); MS (APCI), $(M + 1)^+$ = 259.1.

PREPARATION 11

6-Chloro-5-(3-chloro-propyl)-1,3-dihydro-indol-2-one

6-Chloro-5-(3-chloro-propyl)-1,3-dihydro-indol-2-one was prepared in a similar fashion to that of Preparation 2 from scheme A-2. Yield = 1.15 g (82%); MS (APCI), $(M + 1)^+$ = 244.1.

PREPARATION 12

5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-1,3 dihydro-indol-2-one

5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-1,3-dihydro-indol-2-one was prepared in a similar fashion to that of Preparation 3 from scheme A-3. Yield: 155 mg (16%) MS (APCI), $(M + 1)^+$ = 427.1.

PREPARATION 13

3-{4-[3-(6-Chloro-2,3-dihydro-1H-indol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole

A solution of 5-[3-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-1,3-dihydro-indol-2-one (1.0 g, 2.34 mmol) in THF (40 mL) with stirring at 0°C was treated with BH_3·THF complex (9.4 mL, 9.4 mmol). The reaction was warmed to reflux for 16 hours. The reaction was cooled and treated with a 10% aqueous solution of sodium carbonate (10 mL) and warmed to reflux for 5.0 hours. The reaction was cooled and the layers were separated. The aqueous layers were extracted with ethyl acetate. The combined organics were dried over magnesium sulfate, filtered and the filtrate concentrated. The crude product was eluted through a flash column (1:1 ethyl acetate:methylene chloride) to give the title compound. Yield = 70 mg (7%). MS (APCI), $(M + 1)^+ = 413.1$.

EXAMPLE 50

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone

A solution of 3-{4-[3-(6-chloro-2,3-dihydro-1H-indol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (69 mg) in THF (1.0 mL) with triethylamine (0.03 mL) was treated with acetic anhydride (0.03 ml) and stirred for 4 hours at reflux. The reaction was quenched with water, extracted with ethyl acetate and filter and concentrated *in vacuo*. Yield: 34 mg (45%) MS (APCI), $(M+1)^+ = 455.1$.

PREPARATION 14

3-Methyl-but-2-enoic acid o-tolylamide

To a cold 0.25 M solution of *o*-toluidine (5.0 mL, 46.85 mmole, 1 eq) in dry THF and pyridine (2 eq) was added dropwise neat 3,3-dimethyl-acryloyl chloride and stirred vigorously. The reaction was filtered and the filtrate diluted with EtOAc (equal volume) and washed with H_2O (3x), 1N HCl (2x), sat. Na_2CO_3 (1x), brine (1x), dried ($MgSO_4$), and concentrated to a solid. A mixture of the titled product and its terminal olefin isomer were isolated as a 1:1 mixture. MS (APCI) = 190.1 $[M+H]^+$.

PREPARATION 15

4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

To a solution of 3-methyl-but-2-enoic-acid *o*-tolylamide (7.27 g, 38.41 mmole, 1 eq) in 1,2-dichlorobenzene (50 mL) was added $AlCl_3$ (30.73 g, 230.49 mmole, 6 eq) and the whole mixture heated to 50-70°C. As the reaction reached about 50 °C vigorous gaseous hydrogen chloride (HCl(g)) was released. After the HCl evolution appeared to cease, the reaction was allowed to continue for an additional 10min before cooling. The reaction was cooled and poured into cold H_2O. The heterogeneous mix was extracted with CH_2Cl_2 (3 x 100 mL), dried ($MgSO_4$) and concentrated to an orange oil which was purified by MPLC (30% EtOAc/hexanes) to give the above titled compound (5.357 g, 28.31 mmole, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.16 (d, J = 7.5Hz, 1H), 7.04 (d, J = 7.5Hz, 1H), 6.96 (t, J = 7.5Hz, 1H), 2.48 (s, 2H), 2.30 (s, 3H), 1.32 (s, 6H).

PREPARATION 16

6-(2-Chloro-acetyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

To a solution of 4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (3.545 g, 18.71 mmole, 1 eq) in CS_2 (200 mL) was added chloroacetyl chloride (2.23 mL, 28.06 mmole, 1.5 eq), followed by aluminum chloride (9.98 g, 74.84 mmole, 4 eq) in one portion. The reaction was heated to reflux for 1 h after which thin layer chromatography (TLC) and mass spectroscopy (MS) indicated complete reaction. After cooling, the solvent was decanted and the remaining residue was carefully hydrolyzed with cold H_2O. The resulting precipitate was filtered and dried at 50°C under high vacuum to give titled compound as a tan solid (4.79 g, 18.03 mmole, 96% yield). 100% purity at 254nm; LCMS (APCI) 266.3 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 4.65 (s, 2H), 2.52 (s, 2H), 2.32 (s, 3H), 1.36 (s, 6H).

PREPARATION 17

6-(2-Chloro-ethyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

To a solution of 6-(2-chloro-acetyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (4.79 g, 18.03 mmole, 1.0 eq) in trifluoroacetic acid (100 mL) was added

triethylsilane (7.20 mL, 45.08 mmole, 2.5 eq) and the whole mixture heated to 60°C. After 2 h TLC (30% EtOAc/hexanes) and MS indicated complete reaction. The reaction was cooled and poured over ice. After extracting with CH_2Cl_2 (3 x 100 mL), drying ($MgSO_4$) and concentrating to an oil, the crude was purified by MPLC (30% EtOAc/hexanes) to give the titled compound as a white solid (3.23 g, 12.84 mmole, 71% yield). 100% purity at 254nm; LCMS (APCI) 252.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (bs, 1H), 6.99 (s, 1H), 6.89 (s, 1H), 3.67 (t, J = 7.3Hz, 2H), 2.98 (t, J = 7.3Hz, 2H), 2.46 (s, 2H), 2.21 (s, 3H), 1.30 (s, 6H).

PREPARATION 18

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

A heterogeneous mix of 6-(2-chloro-ethyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (2.200 g, 8.739 mmole, 1.0 eq), sodium carbonate (1.158 g, 10.924 mmole, 1.25 eq), and added 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (3.353 g, 13.110 mmole, 1.5 eq) in water (20 mL) was heated to 175°C under microwave assistance for 10 min. The reaction was diluted with H_2O (100mL), CH_2Cl_2 (100mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2x 50mL) and the organic dried ($MgSO_4$), concentrated, and the residue purified by MPLC (25% EtOAc/CH_2Cl_2 ----- 50% EtOAc gradient over 20min and hold for 20min ---- 100% EtOAc gradient over 20min). Titled product was obtained as a white crystalline solid in 63% yield. 100% purity at 254 nm; LCMS (APCI) 435.2 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, J = 7.94Hz), 7.80 (d, 1H, J = 7.94Hz), 7.46 (t, 1H, J = 7.94Hz), 7.34 (t, 1H, J = 7.94Hz), 7.02 (s, 1H), 6.91 (s, 1H), 4.78 (s, 1H), 3.69-3.55 (m, 4H), 2.86-2.59 (m, 8H), 2.45 (s, 2H), 2.21 (s, 3H), 1.30 (s, 6H).

PREPARATION 19

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline

To a stirring solution of 6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (0.500 g, 1.150 mmole) in dry THF (50

mL) was added Borane THF complex (1 M in THF, 2 eq) and the reaction heated to reflux for 3 h. Upon cooling the reaction was quenched with MeOH and 1 mL acetic acid. The reaction was concentrated to a residue and stripped from MeOH (3x 50 mL). The residue was taken up in CH_2Cl_2, washed with water and the organics dried ($MgSO_4$) and concentrated to a residue. The residue was taken up in dioxane and the HCl salt was precipitated from HCl dioxane treatment. The salt was collected by filtration and then converted to its free base by treatment with NaOH and extraction with EtOAc to give titled product (0.421 g, 1.000 mmole, 87% yield). 100% purity at 254nm; LCMS (APCI) 421.2 [M+H]+; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (s, 6 H) 1.73 (m, 2 H) 2.06 (s, 3 H) 3.05 (m, 6 H) 3.28 (m, 2 H) 3.35 (m, 2 H) 3.72 (d, *J*=13.43 Hz, 2 H) 3.98 (m, 2 H) 6.74 (s, 1 H) 6.93 (d, *J*=0.98 Hz, 1 H) 7.37 (t, *J*=7.69 Hz, 1 H) 7.48 (t, *J*=7.57 Hz, 1 H) 7.84 (dd, *J*=11.72, 8.30 Hz, 2 H).

EXAMPLE 51

1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone hydrochloride

To a solution of 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline (0.499 g, 1.000 mmole) in dry THF (5 mL) was added sodium hydride (NaH) (60% dispersed in oil, 1.1 eq). After stirring for 10 min. at rt, acetyl chloride was added dropwise. The reaction was stirred for 30 min. and was then diluted with H_2O/EtOAc and the layers separated. The organics were dried and concentrated and the residue subjected to MPLC (EtOAc). The HCl salt was precipitated by treatment of an ether solution of free base with 1N HCl in ethyl ether (Et_2O) to give titled product (0.125 g, 0.270 mmole). 100% purity at 254nm; LCMS (APCI) 463.2 [M+H]+; ^{1}H NMR (400 MHz,$CDCl_3$) δ ppm 1.14 (s, 2 H) 1.25 (s, 2 H) 1.32 (d, *J*=8.30 Hz, 3 H) 1.55 (ddd, *J*=13.31, 7.57, 7.45 Hz, 1 H) 1.90 (s, 3 H) 2.11 (s, 1 H) 2.21 (s, 2 H) 2.27 (s, 1 H) 2.68 (m, 2 H) 2.80 (m, 7 H) 3.02 (ddd, *J*=13.00, 7.75, 5.37 Hz, 1 H) 3.59 (m, 4 H) 4.66 (m, 1 H) 6.95 (d, *J*=15.14 Hz, 1 H) 7.03 (dd, *J*=7.82, 1.71 Hz, 1 H) 7.34 (td, *J*=7.57, 0.98 Hz, 1 H) 7.45 (m, 1 H) 7.79 (m, 1 H) 7.90 (d, *J*=8.06 Hz, 1 H).

PREPARATION 20

3-Methyl-but-2-enoic acid (3-chloro-2-methyl-phenyl)-amide

3,3-Diethylacryoyl chloride (21.0 mL, 0.189 mol) was slowly added to a solution of 3-chloro-2-methylaniline (20.0 mL, 0.167 mol) and pyridine (17.0 mL, 0.210 mol) in dichloromethane (210 mL) at 0 °C. After 1.5 h, the reaction was quenched by slow addition of saturated sodium bicarbonate solution (60 mL). The solution was transferred to a separatory funnel and the layers separated. The aqueous layer was back-extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting purple solid was used directly without purification. MS (APCI): $(M+1)^+ = 224.1$.

PREPARATION 21

7-Chloro-6-(2-chloro-acetyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

To a solution of 3-methyl-but-2-enoic acid (3-chloro-2-methyl-phenyl)-amide in CH_2Cl_2 (167 mL) was slowly added aluminum chloride (91.5 g, 0.686 mol) at a rate to maintain gentle reflux. Upon complete addition of the aluminum chloride, a reflux condenser was attached and the reaction was heated to reflux. After 1.5 h, TLC showed no remaining starting material. Chloroacetyl chloride (20.0 mL, 0.250 mol) was slowly added and the mixture was refluxed for an additional 4 h. The reaction mixture was cooled to ambient temperature, poured into ice water (1000 mL) and extracted with CH_2Cl_2 (4 x 300 mL). The organic extracts were combined, washed with saturated sodium chloride solution (200 mL), dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The resulting solid was used directly without purification. MS (APCI): $(M+1)^+ = 300.1$, $(M+3)^+ = 302.1$.

PREPARATION 22

7-Chloro-6-(2-chloro-ethyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

To a solution of 7-chloro-6-(2-chloro-acetyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one in trifluoroacetic acid (168.0 mL) was added triethylsilane (59.0 mL, 0.369 mol). The reaction mixture was heated to 60 °C under nitrogen. After 5.5 h, the reaction was cooled to ambient temperature and the reaction was stirred overnight. The reaction mixture was poured into ice water (350 mL). The reaction flask was

rinsed with methanol (50 mL). The mixture was vigorously stirred resulting in formation of a precipitate. The solid was filtered and then triturated with hexanes. The solid was recrystallized from hot methyl-*tert*-butyl ether (MTBE) (600 mL) to product as a light tan solid. Yield: 36.0345 g (0.126 mol, 75% yield over four steps). MS (APCI): $(M+1)^+ = 288.1$. ^1H NMR (400 MHz, $CDCl_3$)δ 7.50 (br s, 1 H), 7.06 (s, 1 H), 3.71 (t, *J*=7.2 Hz, 2 H), 3.16 (t, *J*=7.2 Hz, 2 H), 2.45 (s, 2 H), 2.30 (s, 3 H), 1.30 (s, 6 H).

PREPARATION 23

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one

A mixture of 7-chloro-6-(2-chloro-ethyl)-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (5.0016 g, 17.476 mmol), 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (4.4811 g, 17.520 mmol), potassium carbonate (4.8299 g, 34.946 mmol) and potassium iodine (0.2903 g, 1.749 mmol) were reacted in acetonitrile (29.0 mL) in a microwave reactor for 1 h at 200 °C. The reaction was cooled to rt, diluted with H_2O and filtered. The solid was washed with H_2O and hexanes. The resulting solid was eluted through a flash column (silica gel 60, 230-400 mesh, 0-3% MeOH in CH_2Cl_2 gradient over 1 h) to give an off-white solid. Yield: 5.6591 g (12.065 mmol, 69%). Anal.: calculated for $C_{25}H_{29}ClN_4OS \cdot 0.02CH_2Cl_2$: C, 63.84; H, 6.22; N, 11.90. Found: C, 63.49, H, 6.13; N, 11.72. LC-MS (APCI): $(M+1)^+ = 471.0$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J*=8.2 Hz, 1 H), 7.80 (d, *J*=8.0 Hz, 1 H), 7.58 (s, 1 H), 7.45 (ddd, *J*=8.0, 7.1, 1.0 Hz, 1 H), 7.34 (ddd, *J*=8.2, 7.1, 1.0 Hz, 1 H), 7.08 (s, 1 H), 3.61 (m, 4 H), 2.98 (m, 2 H), 2.80 (s, 4 H), 2.68 (m, 2 H), 2.44 (s, 2 H), 2.31 (s, 3 H), 1.30 (s, 6 H).

PREPARATION 24

6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline

To a solution of 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-1H-quinolin-2-one (2.5024 g, 5.335 mmol) in anhydrous THF (18 mL) under a nitrogen atmosphere was added borane-THF complex (1.0 M,

6.4 mL, 6.4 mmol). The reaction was refluxed overnight. Additional borane-THF complex (1.0 M, 6.4 mL, 6.4 mmol) was added and the reaction was refluxed for an additional 4 h then cooled to ambient temperature. The excess reagent was quenched by slow addition of methanol (MeOH, 20.0 mL). The reaction mixture was heated to reflux overnight then cooled to ambient temperature. The organic solvents were removed *in vacuo* to give a white residue. The residue was dissolved in MeOH (20 mL) and removed *in vacuo*. The residue was dissolved in methylene chloride (CH_2Cl_2) and washed with saturated sodium bicarbonate solution ($NaHCO_3$, 2 x 30 mL) and the organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated to an oil. The oil was eluted through a flash column (silica gel 60, 230-400 mesh, 0-5% MeOH in CH_2Cl_2 gradient over 1 h) to give an off-white solid. Yield = 1.6876 g (3.709 mmol, 70%).Anal.: calculated for $C_{25}H_{31}ClN_4S \cdot 0.05CH_2Cl_2$: C, 65.50; H, 6.82; N, 12.20. Found: C, 65.14, H, 6.91; N, 11.91. MS (APCI), $(M+1)^+ = 456$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J=8.2 Hz, 1 H), 7.80 (d, J=8.2 Hz, 1 H), 7.45 (t, J=7.4 Hz, 1 H), 7.34 (t, J=7.4 Hz, 1 H), 7.00 (s, 1 H), 3.76 (br s, 1 H), 3.60 (m, 4 H), 3.36 (m, 2 H), 2.90 (m, 2 H), 2.80 (m, 4 H), 2.65 (m, 2 H), 2.17 (s, 3 H), 1.71 (m, 2 H), 1.28 (s, 6 H).

EXAMPLE 52

1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone methane sulfonate

To a stirred solution of 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline (0.4497 g, 0.988 mmol) in THF (10 mL) under a nitrogen atmosphere was added acetyl chloride (77.4 µL, 1.089 mmol). The reaction was stirred overnight. Additional acetyl chloride (0.0250 mL, 0.351 mmol) was added to try to drive the reaction to completion. After 0.5 h, there was no change in TLC. The reaction was quenched by slow addition of sat. $NaHCO_3$ solution (10 mL) and ethyl acetate (EtOAc, 10 mL). The layers were separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was eluted through a flash column (silica gel 60, 230-400 mesh, 25-75% EtOAc in hexanes gradient over 1 h) to a clear oil. Attempts to crystallize using CH_2Cl_2 and CH_2Cl_2/hexanes were unsuccessful. The oil was taken up in THF (9.5

mL) and heated to 40 °C. Methanesulfonic acid (61.5 µL, 0.948 mmol) was added and after 5 min, the reaction was allowed to cool to ambient temperature. The product was allowed to crystallize overnight. Hexanes were added to the reaction mixture and the solid was filtered and washed with hexanes. The wet solid was dried in a vacuum oven at 60 °C to give a white/off-white crystalline solid as the mesylate salt. Yield: 0.4576 g (0.771 mmol, 78%). Anal.: calculated for $C_{27}H_{33}ClN_4OS•CH_4O_3S•0.34H_2O$: C, 56.11; H, 6.34; N, 9.35. Found: C, 55.72, H, 6.01; N, 8.97. MS (APCI), $(M+1)^+ = 498$. ^1H NMR (400 MHz, $CDCl_3$) δ 11.60 (br s, 0.6 H), 11.47 (br s, 0.4 H), 7.84 (m, 2 H), 7.51 (m, 1 H), 7.40 (m, 1 H), 7.35 (s, 0.6 H), 7.32 (s, 0.4 H), 4.65 (m, 0.6 H), 4.16 (m, 1.4 H), 3.97 (m, 2 H), 3.70 (m, 1 H), 3.32 (m, 4 H), 3.01 (m, 1 H), 2.90 (s, 3 H), 2.28 (s, 1.2 H), 2.25 (s, 1.8 H), 2.11 (s, 1 H), 1.90 (m, 1.2 H), 1.85 (s, 2.4 H), 1.81 (s, 3.6 H), 1.75 (m, 1.2 H), 1.55 (m, 0.6 H), 1.35 (s, 1.8 H), 1.33 (s, 1.2 H), 1.25 (s, 1.2 H), 1.14 (s, 1.8 H).

EXAMPLE 53

1-{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-propan-1-one methane sulfonate

To a stirred solution of 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline (0.4500g, 0.989 mmol) in THF (10 mL) under a nitrogen atmosphere was added propionyl chloride (94.6 µL, 1.089 mmol). The reaction was stirred overnight. Additional propionyl chloride (31.0 µL, 0.357 mmol) was added to try to drive the reaction to completion. After 0.5 h, there was no change in TLC. The reaction was quenched by slow addition of sat. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The layers were separated and the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was eluted through a flash column (silica gel 60, 230-400 mesh, 25-75% EtOAc in hexanes gradient over 1 h) to a clear oil. Attempts to crystallize using CH_2Cl_2 and CH_2Cl_2/hexanes were unsuccessful. The oil was taken up in THF (9.0 mL) and heated to 40 °C. Methanesulfonic acid (59.0 µL, 0.909 mmol) was added and after 5 min, the reaction was allowed to cool to ambient temperature. The product was allowed to crystallize overnight. Hexanes were added to the reaction mixture and the solid was filtered and washed with hexanes. The wet solid was dried

in a vacuum oven at 60 °C to give a white/off-white crystalline solid as the mesylate salt. Yield: 0.4484 g (0.738 mmol, 75%). Anal. calculated for $C_{28}H_{35}ClN_4OS•CH_4O_3S$: C, 57.36; H, 6.47; N, 9.23. Found: C, 57.01, H, 6.23; N, 8.90. MS (APCI), $(M+1)^+$ = 512. ^1H NMR (400 MHz, $CDCl_3$) δ 11.58 (br s, 0.6 H), 11.45 (br s, 0.4 H), 7.84 (m, 2 H), 7.51 (m, 1 H), 7.40 (m, 1 H), 7.34 (s, 0.6 H), 7.31 (s, 0.4 H), 4.66 (m, 0.6 H), 4.16 (m, 1.4 H), 3.98 (m, 2 H), 3.71 (m, 1 H), 3.36 (m, 2 H), 3.26 (m, 1 H), 3.00 (m, 0.6 H), 2.90 (s, 3 H), 2.60 (m, 0.4 H), 2.48 (m, 0.4 H), 2.23 (s, 1.8 H), 2.16 (m, 0.6 H), 2.08 (s, 1.2 H), 1.89 (m, 1.4 H), 1.75 (s, 6 H), 1.54 (m, 0.6 H), 1.34 (s, 1.8 H), 1.32 (s, 1.2 H), 1.24 (s, 1.2 H), 1.23 (t, *J*=7.5 Hz, 1.2 H), 1.13 (s, 1.8 H), 1.04 (t, *J*=7.5 Hz, 1.8 H).

EXAMPLE 54

{6-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-3,4-dihydro-2H-quinolin-1-yl}-cyclopropylmethanone

To a stirred solution of 6-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4,8-trimethyl-1,2,3,4-tetrahydro-quinoline (0.4496g, 0.988 mmol) in THF (10 mL) under a nitrogen atmosphere was added cyclopropanecarbonyl chloride (98.8 µL, 1.089 mmol). The reaction was stirred overnight. Additional propionyl chloride (31.0 µL, 0.342 mmol) was added to try to drive the reaction to completion. After 0.5 h, there was no change in TLC. The reaction was quenched by slow addition of sat. $NaHCO_3$ solution (10 mL) and EtOAc (10 mL). The layers were separated and the organic layer was dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was eluted through a flash column (silica gel 60, 230-400 mesh, 25-75% EtOAc in hexanes gradient over 1 h) to give a white foam. The foam was dried overnight under high vacuum. Yield: 0.4477 g (0.856 mmol, 87%). Anal. calculated for $C_{29}H_{35}ClN_4OS•0.07CH_2Cl_2$: C, 65.99; H, 6.69; N, 10.49. Found: C, 65.87, H, 6.50; N, 10.19. MS (APCI), $(M+1)^+$ = 524. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=8.1 Hz, 1 H), 7.81 (d, *J*=8.1 Hz, 1 H), 7.46 (ddd, *J*=8.1, 7.0, 1.0 Hz, 1 H), 7.35 (ddd, *J*=8.1, 7.0, 1.0 Hz, 1 H), 7.14 (s, 0.9 H), 7.08 (s, 0.1 H), 4.65 (m, 1 H), 3.60 (m, 4 H),) 3.04 (m, 2 H), 2.81 (m, 4 H), 2.71 (m, 2 H), 2.34 (s, 2.7 H), 2.10 (s, 0.3 H), 1.91 (m, 1 H), 1.58 (m, 3 H), 1.37 (m, 3 H), 1.21 (s, 0.3H), 1.17 (s, 2.7 H), 1.05 (m, 2 H), 0.83 (m, 1 H), 0.55 (m, 1 H).

PREPARATION 25

7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

A. 1,3,4,5-tetrahydro-benzo[b]azepin-2-one

Beilstein Registry Number 137258; CAS Registry Number 4424-80-0

Horning, E. C.; Stromberg, V. L.; Lloyd, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 5153-5155.

B. 7-(2-Chloro-acetyl)-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

To a 1-L round-bottom flask was added $AlCl_3$ (83.4 g, 626 mmol), CS_2 (500 mL), chloroacetyl chloride (12.0 mL, 156.4 mmol), and azepinone (from step A) [16.79 g, 104.3 mmol]. The reaction was stirred to a thick gummy deposit, refluxed for 3 h and cooled to 0°C. The solvent was decanted and ice water (300 mL) was added very slowly (CAUTION: exotherm and HCl gas produced) until a solid suspension was formed. The solid was collected by filtration and washed with H_2O (50 mL) to produce a brown solid. This material was recrystallized in methanol/H_2O to give the title compound (19.2 g, 78%) as a dark tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 7.87-7.81 (m, 2 H), 7.10 (d, J = 9.0 Hz, 1 H), 4.68 (s, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 2.42 (t, J = 7.2 Hz, 2 H), 2.36-2.25 (m, 2 H).

C. 7-(2-Chloro-ethyl)-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

Into a 250-mL round-bottom flask was placed the ketone from step B (5.00 g, 21.1 mmol) and TFA (25 mL). The solution was cooled to 0 °C and triethylsilane (10.2 mL, 63.2 mmol) was added dropwise over a 5 min period. The reaction was warmed to 50 °C and stirred for 18 h. The mixture was cooled to rt, diluted with H_2O (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under high vacuum to produce the title compound (5.1 g, >99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 7.17-7.12 (m, 2 H), 7.00 (d, J = 9.0 Hz, 1 H), 3.72 (t, J = 9.0 Hz, 2 H), 3.06 (t, J = 7.2 Hz, 2 H), 2.80 (t, J = 7.2 Hz, 2 H), 2.41-2.28 (m, 4 H).

D. 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

A suspension of the compound from step C (1.00 g, 4.48 mmol) in CH_3CN (40 mL) was treated with 3-piperazin-1-yl-benzo[*d*]isoxazole • HCl (1.20 g, 4.98 mmol), NaI

(744 mg, 4.96 mmol), and potassium carbonate (K_2CO_3) (1.87 g, 13.5 mmol). The mixture was heated to reflux under nitrogen (N_2) for 44 h, then allowed to cool. The mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were dried over Na_2SO_4, decanted, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, EtOAc) to give the title compound (0.95 g, 54%) as a white powder: mp 199-200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1 H), 7.45-7.52 (m, 2 H), 7.19-7.25 (m, 1 H), 7.18 (s, 1 H), 7.08-7.11 (m, 2 H), 6.88 (d, J = 8.4 Hz, 1 H), 3.61-3.64 (m, 4 H), 2.65-2.86 (m, 10 H), 2.35 (t, J = 7.5 Hz, 2 H), 2.23 (m, 2 H); ESI MS *m/z* 391 $[C_{23}H_{26}N_4O_2 + H]^+$; R_f 0.41 (silica gel, 95:5 EtOAc/MeOH); HPLC 97.0% (AUC), t_R = 11.36 min. Anal. Calc'd for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.71; H, 6.72; N, 14.28.

EXAMPLE 55

1-{7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl}-ethanone methanesulfonate

A. 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine

A suspension of the title compound of Preparation 25 (0.36 g, 0.92 mmol) in THF (8 mL) was treated with a solution of BH_3 in THF (4.0 mL, 1.5 M, 6.0 mmol). The resulting clear solution was heated to reflux for 3 h, then allowed to cool. The reaction was quenched with 6N HCl until gas evolution subsided. The mixture was heated to reflux for 1 h, allowed to cool, and then made basic (pH 8) with solid sodium hydroxide (NaOH) and a 1N NaOH solution. The biphasic mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, 2:1 hexanes/EtOAc) to give the title compound (0.22 g, 63%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1 H), 7.44-7.52 (m, 2 H), 7.19-7.25 (m, 1 H), 6.96 (d, J = 1.7 Hz, 1 H), 6.89 (dd, J = 7.9, 2.0 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H), 3.71 (bs, 1 H), 3.61-3.64 (m, 4 H), 3.02 (t, J = 5.3 Hz, 2 H), 2.62-2.78 (m, 10 H),

1.76-1.83 (m, 2 H), 1.60-1.67 (m, 2 H); ESI MS *m/z* 377 $[C_{23}H_{28}N_4O + H]^+$; R_f 0.52 (silica gel, 1:1 hexanes/EtOAc).

B. 1-{7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl}-ethanone methanesulfonate

A solution of the title compound from step A (0.22 g, 0.58 mmol) in CH_2Cl_2 (12 mL) was treated with acetic anhydride (Ac_2O) (55 µL, 0.58 mmol). After stirring at rt under N_2 for 15 h, the reaction was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, decanted, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, 2:1 EtOAc/hexanes) to give a white solid residue (0.21 g, 0.50 mmol, 86%). The residue was dissolved in EtOAc (15 mL) and treated with methanesulfonic acid (CH_3SO_3H) (2 M in Et_2O, 0.25 mL, 1 mmol). After stirring for 5 min, the resulting precipitate was isolated by filtration, washed with Et_2O (3 x 6 mL), and dried in a vacuum oven at 50 °C for 4 days to give the title compound (228 mg, 88%) as a white powder: mp 234-235 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.99 (s, 1 H), 7.51-7.63 (m, 3 H), 7.27-7.33 (m, 1 H), 7.13-7.17 (m, 2 H), 7.08 (d, *J* = 7.8 Hz, 1 H), 4.68 (m, 1 H), 4.20 (d, *J* = 14.5 Hz, 2 H), 3.99 (t, *J* = 12.3 Hz, 2 H), 3.72 (d, *J* = 12.2 Hz, 2 H), 3.08-3.33 (m, 6 H), 2.90 (s, 3 H), 2.68-2.74 (m, 2 H), 2.50-2.59 (m, 1 H), 1.74-1.99 (m, 3 H), 1.83 (s, 3 H), 1.32-1.40 (m, 1 H); ESI MS *m/z* 419 $[C_{25}H_{30}N_4O_2 + H]^+$; R_f 0.47 (silica gel, 95:5 EtOAc/MeOH); HPLC >99% (AUC), t_R = 12.12 min. Anal. Calc'd for $C_{25}H_{30}N_4O_2 \cdot CH_3SO_3H$: C, 60.68; H, 6.66; N, 10.89. Found: C, 60.62; H, 6.57; N, 10.82.

PREPARATIONS 26A and 26B

7-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-1,3,4,5-tetrahydro-benzo[b]azepin-2-one (Prep. 26A)

A suspension of 7-chloroethylazepin-2-one (1.71 g, 7.64 mmol) and 5-fluoro-3-piperazin-1-yl-benzo[*d*]isothiazole (1.99 g, 8.39 mmol) in CH_3CN (80 mL) was treated with NaI (1.27 g, 8.47 mmol), and K_2CO_3 (2.12 g, 15.3 mmol). The mixture was heated to reflux under N_2 for 3 days, then allowed to cool. The mixture was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The

residue was purified by flash column chromatography (silica gel, 2:1 EtOAc/hexanes) to give an off-white solid (2.58 g, 79%). The solid was recrystallized from EtOAc/hexanes to give the title compound as a white fluffy solid: mp 168-169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.9, 4.6 Hz, 1 H), 7.54 (dd, J = 9.3, 2.2 Hz, 1 H), 7.23-7.29 (m, 2 H), 7.09-7.12 (m, 2 H), 6.89 (d, J = 8.4 Hz, 1 H), 3.54-3.57 (m, 4 H), 2.67-2.85 (m, 10 H), 2.34-2.36 (m, 2 H), 2.21-2.26 (m, 2 H); ESI MS *m/z* 425 $[C_{23}H_{25}FN_4OS + H]^+$; R_f 0.31 (silica gel, EtOAc); HPLC >99% (AUC), t_R = 12.28 min. Anal. Calcd for $C_{23}H_{25}FN_4OS$: C, 65.07; H, 5.94; N, 13.20. Found: C, 64.94; H, 5.97; N, 13.13.

7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-1,3,4,5-tetrahydro-benzo[b]azepin-2-one (Prep. 26B)

A suspension of 7-chloroethylazepin-2-one (1.49 g, 6.66 mmol) and 7-fluoro-3-piperazin-1-yl-benzo[*d*]isothiazole • HCl (2.00 g, 7.31 mmol) in CH_3CN (70 mL) was treated with NaI (1.10 g, 7.34 mmol), and K_2CO_3 (2.77 g, 20.0 mmol). The mixture was heated to reflux under N_2 for 3 days, then allowed to cool. The mixture was diluted with H_2O (200 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 4:1 EtOAc/hexanes) to give the title compound (2.54 g, 90%) as an off-white solid: mp 180-181 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1 H), 7.31-7.37 (m, 1 H), 7.09-7.17 (m, 4 H), 6.88 (d, J = 8.5 Hz, 1 H), 3.59-3.62 (m, 4 H), 2.66-2.87 (m, 10 H), 2.34-2.36 (m, 2 H), 2.21-2.25 (m, 2 H); ESI MS *m/z* 425 $[C_{23}H_{25}FN_4OS + H]^+$; R_f 0.22 (silica gel, EtOAc); HPLC >99% (AUC), t_R = 12.79 min. Anal. Calc'd for $C_{23}H_{25}FN_4OS$: C, 65.07; H, 5.94; N, 13.20. Found: C, 64.86; H, 5.86; N, 13.01.

EXAMPLE 56

1-(7-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone: compound with methane sulfonic acid

A. 7-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-1H-benzo[b]azepine

A suspension of the title compound of Preparation 26A (1.46 g, 3.44 mmol) in THF (10 mL) was treated dropwise with a solution of BH_3 in THF (22 mL, 1.0M, 22 mmol). The mixture was heated at reflux for 3 h, then allowed to cool. The reaction was quenched with 6N HCl until gas evolution subsided. The mixture was heated at reflux for 30 min, allowed to cool, and then made basic (pH ~8-9) with solid NaOH and 1 N NaOH. The biphasic mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, gradient from 2:1 to 1:1 hexanes/EtOAc) to give the title compound (0.53 g, 38%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 11.56 (bs, 1 H), 7.82-7.86 (m, 2 H), 7.49-7.54 (m, 1 H), 7.40-7.43 (m, 1 H), 6.88 (s, 1 H), 6.75 (s, 1 H), 4.03-4.11 (m, 4 H), 3.46-3.70 (m, 2 H), 3.04-3.36 (m, 8 H), 2.91-2.97 (m, 4 H), 2.89 (s, 3 H), 2.69-2.73 (m, 2 H), 1.86 (bm, 2 H), 1.70 (bm, 2 H); ESI MS *m/z* 419 $[C_{25}H_{30}N_4S + H]^+$; R_f 0.34 (silica gel, 1:1 EtOAc/hexanes).

B. <u>1-(7-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone: compound with methane sulfonic acid</u>

A solution of the title compound from step A (0.53 g, 1.29 mmol) in CH_2Cl_2 (15 mL) was treated with acetic anhydride (0.13 mL, 1.4 mmol) under N_2. After stirring at rt overnight, saturated $NaHCO_3$ (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, gradient from 2:1 to 3:1 EtOAc/hexanes) to give a white semi-solid (0.53 g, 91%). The semi-solid (0.53 g, 1.2 mmol) was dissolved in EtOAc (30 mL) and treated with CH_3SO_3H (2M in Et_2O, 0.59 mL, 1.2 mmol). After stirring for 30 minutes (min), the resulting precipitate was isolated by filtration, washed with Et_2O (3 x 10 mL), and dried in a vacuum oven at 55 °C overnight to give the title compound (0.49 g, 76%) as a white powder: mp 188-191 °C (dec); ^1H NMR (300 MHz, $CDCl_3$) δ 11.86 (s, 1 H), 7.50-7.64 (m, 3 H), 7.28-7.33 (m, 2 H), 7.15 (dd, J = 7.9, 1.9 Hz, 1 H), 7.01 (d, J = 7.9 Hz, 1 H), 4.73-4.77 (m, 1 H), 4.21 (d, J = 14.6 Hz, 2 H), 3.95-4.04 (m, 2 H), 3.74 (d, J = 11.4 Hz, 2 H), 3.10-3.35 (m, 6 H), 2.91 (s, 3 H), 2.47-2.57 (m, 1 H), 2.14-2.26 (m, 2 H), 1.85-1.95 (m, 1 H), 1.45-1.74 (m, 3 H),

1.42 (s, 3 H), 1.17 (s, 3 H), 1.07 (t, J = 7.4 Hz, 3 H); ESI MS m/z 461 [$C_{28}H_{36}N_4O_2$ + H]$^+$; R_f 0.66 (silica gel, 2:1 EtOAc/hexanes); HPLC 98.4% (AUC), t_R = 13.67 min. Anal. Calc'd for $C_{28}H_{36}N_4O_2 \bullet CH_3SO_3H \bullet 1.2H_2O$: C, 60.23; H, 7.39; N, 9.69. Found: C, 60.24; H, 7.40; N, 9.49.

EXAMPLE 57

1-(7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone; compound with methanesulfonic acid

A. 7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-1H-benzo[b]azepine

A suspension of the title compound from Preparation 26B (1.02 g, 2.40 mmol) in THF (10 mL) was treated dropwise with a solution of BH_3 in THF (15 mL, 1.0 M, 15 mmol). The mixture was heated at reflux for 2.5 h, then allowed to cool. The reaction was quenched with 1N HCl until gas evolution subsided. The mixture was heated at reflux for 30 min, allowed to cool, and then made basic (pH ~8-9) with 1 N NaOH. The biphasic mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, 1:1 hexanes/EtOAc) to give the title compound (0.79 g, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (bs, 1 H), 7.82-7.86 (m, 2 H), 7.49-7.54 (m, 1 H), 7.40-7.43 (m, 1 H), 6.88 (s, 1 H), 6.75 (s, 1 H), 4.03-4.11 (m, 4 H), 3.46-3.70 (m, 2 H), 3.04-3.36 (m, 8 H), 2.91-2.97 (m, 4 H), 2.89 (s, 3 H), 2.69-2.73 (m, 2 H), 1.86 (bm, 2 H), 1.70 (bm, 2 H); ESI MS m/z 419 [$C_{25}H_{30}N_4S$ + H]$^+$; R_f 0.34 (silica gel, 1:1 EtOAc/hexanes).

B. 1-(7-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl)-ethanone; compound with methanesulfonic acid

A solution of the title compound from step A (0.72 g, 1.75 mmol) in CH_2Cl_2 (20 mL) was treated with acetic anhydride (0.17 mL, 1.8 mmol) under N_2. After stirring at rt overnight, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and the

solvent was removed in vacuo. The residue was purified by flash column chromatography (silica gel, 4:1 EtOAc/hexanes) to give a white semi-solid (0.60 g, 76%). The semi-solid (0.60 g, 1.3 mmol) was dissolved in EtOAc (20 mL) and treated with CH_3SO_3H (2M in Et_2O, 0.66 mL, 1.3 mmol). After stirring for 10 min, the clear solution was diluted with Et_2O (20 mL) to give a gummy precipitate. After stirring for 10 min, the solvent was removed in vacuo to give a gummy residue. The residue was suspended in Et_2O (40 mL), and the mixture was stirred until the residue became particulate. The solid was isolated by filtration, washed with Et_2O (4 x 20 mL), and dried in a vacuum oven at 45 °C overnight to give the title compound (0.62 g, 85%) as a white powder: mp 188-191 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.86 (s, 1 H), 7.50-7.64 (m, 3 H), 7.28-7.33 (m, 2 H), 7.15 (dd, J = 7.9, 1.9 Hz, 1 H), 7.01 (d, J = 7.9 Hz, 1 H), 4.73-4.77 (m, 1 H), 4.21 (d, J = 14.6 Hz, 2 H), 3.95-4.04 (m, 2 H), 3.74 (d, J = 11.4 Hz, 2 H), 3.10-3.35 (m, 6 H), 2.91 (s, 3 H), 2.47-2.57 (m, 1 H), 2.14-2.26 (m, 2 H), 1.85-1.95 (m, 1 H), 1.45-1.74 (m, 3 H), 1.42 (s, 3 H), 1.17 (s, 3 H), 1.07 (t, J = 7.4 Hz, 3 H); ESI MS *m/z* 461 $[C_{28}H_{36}N_4O_2 + H]^+$; R_f 0.66 (silica gel, 2:1 EtOAc/hexanes); HPLC 98.4% (AUC), t_R = 13.67 min. Anal. Calcd for $C_{28}H_{36}N_4O_2 \cdot CH_3SO_3H \cdot 1.2H_2O$: C, 60.23; H, 7.39; N, 9.69. Found: C, 60.24; H, 7.40; N, 9.49.

PREPARATION 27

7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-1,3,4,5-tetrahydro-benzo[b]azepin-2-one

A. 4,4-Dimethyl-3,4-dihydro-2*H*-naphthalen-1-one

Beilstein Registry Number 1818110; CAS Registry Number 2979-69-3

Endo, Y.; Takehana, S.; Ohno, M.; Driedger, P. E.; Stabel, S.; Mizutani, M. Y.; Tomioka, N.; Itai, A.; Shudo, K. *J. Med. Chem.* **1998**, *41*, 1476-1496.

B. 4,4-Dimethyl-3,4-dihydro-2H-naphthalen-1-one oxime

Beilstein Registry Number 1818110; CAS Registry Number 2979-69-3

Woods, G. F.; Heying, T. L.; Schwartzman, L. H.; Grenell, S. M.; Gasser, W. F.; Rowe, E. W.; Bolgiano, N. C. *J. Org. Chem.* **1954**, *19*, 1290-1295. Into a 1-L round-bottom flask was placed the tetralone from step A (8.94 g, 51.4 mmol), hydroxylamine hydrochloride (4.29 g, 61.7 mmol), sodium acetate (8.43 g, 103

mmol), and 50% aqueous ethanol (350 mL). The mixture was refluxed for 16 h, cooled to rt and made alkaline by the addition of 10% aqueous $NaHCO_3$. The reaction was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to produce the title oxime (8.37 g, 84%) as an orange solid.

C. 5,5-Dimethyl-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

Into a 500-mL round-bottom flask equipped with a mechanical stirrer was placed polyphosphoric acid (90 g). The reaction was heated to 125°C, the title compound from step B (8.37 g, 44.3 mmol) was added in one portion, and the reaction was stirred for 5 min. The mixture was poured into ice water (300 mL), stirred until the polyphosphoric acid was dissolved and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to produce the title benzazepinone (7.76 g, 93%) as a tan solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (bs, 1 H), 7.42 (dd, J = 7.7, 1.7 Hz, 1 H), 7.13-7.25 (m, 2 H), 6.91 (dd, J = 7.6, 1.6 Hz, 1 H), 2.40 (t, J = 7.0 Hz, 2 H), 2.11 (t, J = 7.0 Hz, 2 H), 1.42 (s, 6 H); ESI MS *m/z* 190 $[C_{12}H_{15}NO + H]^+$.

D. 7-(2-Chloro-acetyl)-5,5-dimethyl-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

Into a 500-mL round-bottom flask equipped with a mechanical stirrer was placed aluminum chloride (33.6 g, 252 mmol), anhydrous dichloromethane (230 mL), chloroacetyl chloride (4.87 mL, 61.05 mmol), and the title compound from step C (7.69 g, 40.7 mmol). The reaction was slowly heated to reflux and stirred for 15 h. The mixture was cooled to 0°C and ice water (200 mL) was slowing added (CAUTION: exotherm). The two layers were separated and the aqueous layer was extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with H_2O (150 mL), dried over Na_2SO_4, concentrated under vacuum, and chromatographed (silica, 4:1 hexanes/ethyl acetate) to produce the title compound (3.82 g, 35%) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1 H), 8.09 (d, J = 1.9 Hz, 1 H), 7.80 (dd, J = 8.2, 2.0 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 1 H), 4.68 (s, 2 H), 2.49 (t, J = 6.5 Hz, 2 H), 2.15 (t, J = 8.3 Hz, 2 H), 1.46 (s, 6 H).

E. 7-(2-Chloro-ethyl)-5,5-dimethyl-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

Into a 100-mL round-bottom-flask was placed the ketone from step D (2.23 g, 8.4 mmol) and TFA (16 mL). The solution was cooled to 0°C and triethylsilane (4.07 mL,

25.2 mmol) was added dropwise over a 5 min period. The reaction was warmed to 50°C and stirred for 15 h. The mixture was cooled to rt, diluted with H_2O (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated under high vacuum and chromatographed (silica, 4:1 hexanes/ethyl acetate) to produce the title compound (1.58 g, 75%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (s, 1 H), 7.24 (d, *J* = 1.8 Hz, 1 H), 7.08 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 3.71 (t, *J* = 7.3 Hz, 2 H), 3.06 (t, *J* = 7.3 Hz, 2 H), 2.39 (t, *J* = 6.8 Hz, 2 H), 2.11 (t, *J* = 7.4 Hz, 2 H), 1.40 (s, 6 H).

F. 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one

A suspension of the title compound from step E (2.55 g, 10.1 mmol) in CH_3CN (100 mL) was treated with 3-piperazin-1-yl-benzo[*d*]isoxazole • HCl (2.68 g, 11.2 mmol), NaI (1.68 g, 11.2 mmol), and K_2CO_3 (4.22 g, 30.5 mmol). The mixture was heated to reflux under N_2 for 87 h, then allowed to cool. The mixture was diluted with H_2O (250 mL) and extracted with CH_2Cl_2 (4 x 200 mL). The combined organic layers were dried over Na_2SO_4, decanted, and the solvent was removed*in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to give the title compound (3.09 g, 73%) as a white powder: mp 193-194°C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 1 H), 7.44-7.52 (m, 2 H), 7.20-7.28 (m, 2 H), 7.15 (s, 1 H), 7.08 (dd, *J* = 7.9, 1.9 Hz, 1 H), 6.82 (d, *J* = 7.9 Hz, 1 H), 3.61-3.65 (m, 4 H), 2.82-2.87 (m, 2 H), 2.73-2.76 (m, 4 H), 2.65-2.70 (m, 2 H), 2.39 (t, *J* = 7.0 Hz, 2 H), 2.10 (t, *J* = 7.0 Hz, 2 H), 1.41 (s, 6 H); ESI MS *m/z* 419 $[C_{25}H_{30}N_4O_2 + H]^+$; R_f 0.55 (silica gel, EtOAc); HPLC 96.4% (AUC), t_R = 12.12 min. Anal. Calc'd for $C_{25}H_{30}N_4O_2 \cdot 0.2H_2O$: C, 71.13; H, 7.26; N, 13.27. Found: C, 71.11; H, 7.30; N, 13.06.

EXAMPLE 60

{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-(4-fluoro-phenyl)-methanone; compound with methanesulfonic acid

A. 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine

A suspension of 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-1,3,4,5-tetrahydro-benzo[*b*]azepin-2-one (3.09 g, 7.38 mmol) in THF (50 mL) was treated with borane (1.5 M in THF, 35.0 mL, 52.5 mmol) over 10 min. The resulting clear solution was heated to reflux under N_2 for 3.5 h, then allowed to cool. The reaction was quenched with 6N HCl until gas evolution subsided. The mixture was heated to reflux for 45 min, allowed to cool, and then made basic with solid NaOH and a 1N NaOH solution (50 mL). The biphasic mixture was extracted with CH_2Cl_2 (4 x 50 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:1 hexanes/EtOAc) to give the title compound (2.42 g, 81%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1 H), 7.45-7.48 (m, 2 H), 7.18-7.24 (m, 1 H), 7.16 (d, J = 1.9 Hz, 1 H), 6.88 (dd, J = 7.8, 2.0 Hz, 1 H), 6.62 (d, J = 7.8 Hz, 1 H), 3.61-3.64 (m, 4 H), 3.00 (t, J = 5.6 Hz, 2 H), 2.62-2.81 (m, 8 H), 1.82-1.90 (m, 2 H), 1.60-1.64 (m, 2 H), 1.38 (s, 6 H); ESI MS *m/z* 405 $[C_{25}H_{32}N_4O + H]^+$; R_f 0.39 (silica gel, 2:1 hexanes/EtOAc).

B. 1-{7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl}-ethanone methanesulfonate

A solution of the title compound from step A (0.90 g, 2.2 mmol) in CH_2Cl_2 (20 mL) was treated with Ac_2O (0.21 mL, 2.2 mmol). After stirring at rt under N_2 for 18 h, the reaction was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:1 EtOAc/hexanes to 3:1 EtOAc/hexanes to EtOAc) to give a white solid residue (0.58 g, 1.30 mmol, 58%). The residue was dissolved in EtOAc (6.5 mL) and treated with CH_3SO_3H (2M in Et_2O, 0.65 mL, 1.3 mmol). After stirring for 45 min, the oily, precipitous mixture was diluted with EtOAc (6.5 mL).

After stirring for an additional 19 h, the resulting precipitate was isolated by filtration, washed with Et_2O (3 x 20 mL), and dried in a vacuum oven at 60°C overnight to give the title compound (595 mg, 84%) as a white powder: mp 227-229°C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.94 (s, 1 H), 7.62 (d, J = 8.0 Hz, 1 H), 7.50-7.59 (m, 2 H), 7.27-7.33 (m, 2 H), 7.16 (dd, J = 7.9, 1.9 Hz, 1 H), 7.02 (d, J = 7.9 Hz, 1 H), 4.71-4.75 (m, 1 H), 4.21 (d, J = 14.6 Hz, 2 H), 3.96-4.04 (m, 2 H), 3.74 (d, J = 11.7 Hz, 2 H), 3.12-3.35 (m, 6 H), 2.90 (s, 3 H), 2.48-2.52 (m, 1 H), 2.15-2.20 (m, 1 H), 1.86 (s, 3 H), 1.47-1.74 (m, 3 H), 1.43 (s, 3 H), 1.20 (s, 3 H); ESI MS *m/z* 447 $[C_{27}H_{34}N_4O_2 + H]^+$; R_f 0.64 (silica gel, EtOAc); HPLC >99% (AUC), t_R = 12.97 min. Anal. Calc'd for $C_{27}H_{34}N_4O_2 \cdot CH_3SO_3H \cdot 0.3H_2O$: C, 61.36; H, 7.10; N, 10.22. Found: C, 61.42; H, 7.13; N, 10.17.

C. {7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl}-(4-fluoro-phenyl)-methanone methanesulfonate

A solution of the title compound from step B (0.90 g, 2.2 mmol) in CH_2Cl_2 (20 mL) under N_2 was cooled in an ice bath, treated Et_3N (0.34 mL, 2.42 mmol) and *p*-fluorobenzoyl chloride (0.26 mL, 2.2 mmol), and warmed to rt. After stirring at rt for 17 h, the reaction was quenched with saturated $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 7:3 hexanes/EtOAc) to give a colorless residue (0.74 g, 1.40 mmol, 63%). The residue (0.71 g, 1.35 mmol) was dissolved in EtOAc (13 mL) and treated with CH_3SO_3H (2M in Et_2O, 0.67 mL, 1.34 mmol). After stirring for 21 h, the clear solution was treated with Et_2O (20 mL). After stirring for 45 min, the oily, precipitous mixture was treated with Et_2O (10 mL) and stirred for an additional 27 h. The mixture was concentrated *in vacuo*, and the resulting oily solid was suspended in Et_2O. The solid was isolated by filtration, washed with Et_2O, and dried in a vacuum oven at 60 °C for 4 d to give the title compound (629 mg, 75%) as a white powder: mp 135-140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.91 (s, 1 H), 7.50-7.62 (m, 4 H), 7.21-7.36 (m, 3 H), 6.78-6.85 (m, 3 H), 6.50 (d, J = 7.9 Hz, 1 H), 5.02-5.06 (m, 1 H), 4.19 (d, J = 13.9 Hz, 2 H), 3.98 (t, J = 13.4 Hz, 2 H), 3.69 (d, J = 11.2 Hz, 2 H), 3.05-3.26 (m, 6 H), 2.88 (s, 3 H), 2.72 (t, J = 11.7 Hz, 1 H), 2.23-2.28 (m, 1H), 1.77-

1.90 (m, 2H), 1.55-1.64 (m, 1H), 1.50 (s, 3H), 1.49 (s, 3H); ESI MS *m/z* 527 $[C_{32}H_{35}FN_4O_2 + H]^+$; R_f 0.77 (silica gel, 2:1 EtOAc/hexanes); HPLC >99% (AUC), t_R = 15.23 min. Anal. Calc'd for $C_{32}H_{35}FN_4O_2 \cdot CH_3SO_3H \cdot H_2O$: C, 61.86; H, 6.45; N, 8.74. Found: C, 61.89; H, 6.40; N, 8.67.

EXAMPLE 61

1-{7-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-propan-1-one; compound with methanesulfonic acid

A solution of the product of Example 60, step A, 7-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-5,5-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (0.45 g, 1.1 mmol) in CH_2Cl_2 (10 mL) under N_2 was cooled in an ice bath, treated with Et_3N (0.17 mL, 1.2 mmol) and propionyl chloride (0.10 mL, 1.1 mmol), and warmed to rt. After stirring at rt for 23 h, additional propionyl chloride (0.10 mL, 1.1 mmol) was added. After stirring for an additional 8 h, the reaction was quenched with saturated $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:1 EtOAc/hexanes) to give a colorless residue (0.40 g, 0.87 mmol, 79%). The residue (0.40 g, 0.87 mmol) was dissolved in EtOAc (10 mL) and treated with CH_3SO_3H (2 M in Et_2O, 0.43 mL, 0.86 mmol). After stirring for 15 min, the clear solution was treated with Et_2O (30 mL). After stirring for 20 min, the oily, precipitous mixture was concentrated *in vacuo*, and the resulting oily solid was suspended in Et_2O (15 mL). After stirring for 16 h, the solid was isolated by filtration, washed with Et_2O (3 x 10 mL), and dried in a vacuum oven at 60 °C for 24 h to give the title compound (416 mg, 86%) as a white powder: mp 188-191 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.86 (s, 1 H), 7.50-7.64 (m, 3 H), 7.28-7.33 (m, 2 H), 7.15 (dd, *J* = 7.9, 1.9 Hz, 1 H), 7.01 (d, *J* = 7.9 Hz, 1 H), 4.73-4.77 (m, 1 H), 4.21 (d, *J* = 14.6 Hz, 2 H), 3.95-4.04 (m, 2 H), 3.74 (d, *J* = 11.4 Hz, 2 H), 3.10-3.35 (m, 6 H), 2.91 (s, 3 H), 2.47-2.57 (m, 1 H), 2.14-2.26 (m, 2 H), 1.85-1.95 (m, 1 H), 1.45-1.74 (m, 3 H), 1.42 (s, 3 H), 1.17 (s, 3 H), 1.07 (t, *J* = 7.4 Hz, 3 H); ESI MS *m/z* 461 $[C_{28}H_{36}N_4O_2 + H]^+$; R_f 0.66 (silica gel, 2:1 EtOAc/hexanes);

HPLC 98.4% (AUC), t_R = 13.67 min. Anal. Calc'd for $C_{28}H_{36}N_4O_2 \bullet CH_3SO_3H \bullet 1.2H_2O$: C, 60.23; H, 7.39; N, 9.69. Found: C, 60.24; H, 7.40; N, 9.49.

PREPARATION 28

6-(2-Chloroacetyl)-3,3-dimethyl-3,4-dihydro-1H-quinolin-2-one

3,3-Dimethyl-3,4-dihydro-1H-quinolin-2-one was prepared according to the procedure in *J. Med. Chem.*, **1986**, *29*, 1832, and underwent a Friedel-Crafts acylation with chloroacetyl chloride according to the procedure described in Preparation 1 to give the title compound as a solid. MS (APCI): $(M + 1)^+ = 252$.

PREPARATION 29

6-(2-Chloro-ethyl)-3,3-dimethyl-3,4-dihydro-1H-quinolin-2-one

To a mixture of the title compound of Preparation 28 (6.52 g, 0.026 mol) and trifluoroacetic acid (20 ml, 0.26 mol), cooled to 0°C under nitrogen, was added portionwise triethylsilane (9.57 ml, 0.059 mol). The reaction mixture was heated at 40-45 °C for 20 minutes and then stirred at rt for 16 hours. The solution was poured into ice water layered with hexane and vigorously stirred for several hours. The precipitate that formed was collected and washed with water and hexanes to give the title compound as a solid. MS (APCI): $(M + 1)^+ = 238$.

PREPARATION 30

6-(2-Chloro-ethyl)-3,3-dimethyl-1,2,3,4-tetrahydro-quinoline

To a solution of 6-(2-chloroethyl)-3,3-dimethyl-3,4-dihydro-1H-quinolin-2-one (1.0 g, 4.21 mmol) in anhydrous THF (75 ml) under nitrogen was added 1.0 M borane-THF complex (14.3 ml, 14.3 mmol). The reaction mixture was refluxed for 1.5 hours and cooled to ambient temperature. The excess reagent was quenched with water and the organic solvent was removed *in vacuo*. The aqueous residue was extracted with methylene chloride and the organic extract was dried over magnesium sulfate, filtered, and concentrated to an oil. Yield = 942 mg (100%); MS (APCI), $(M + 1)^+ = 224$. ^{1}H-NMR ($CDCl_3$) δ 6.80 (d, J = 8.1 Hz, 1 H), 6.75 (s, 1H), 6.43 (d, J = 8.1 Hz, 1 H), 3.87 (br s, 1H), 3.62 (t, J = 7.6, 8.1 Hz, 2 H), 2.88 (m, 4 H), 2.45 (s, 2 H), 0.99 (s, 6 H).

PREPARATION 31

1-[6-(2-Chloro-ethyl)-3,3-dimethyl-3,4-dihydro-2H-quinolin-1-yl]-ethanone

A mixture of 6-(2-chloroethyl)-3,3-dimethyl-1,2,3,4-tetrahydroquinoline (942 mg, 4.21 mmol) and acetyl chloride (0.317 ml, 4.44 mmol) in dry acetone (15 ml) was refluxed for 2 hours. The reaction mixture was poured into dilute aqueous HCl (100 ml) and the whole extracted with chloroform. The organic extract was dried over magnesium sulfate, filtered, and concentrated. The product was washed with hexane to give an off-white, crystalline solid. Yield = 791 mg (71%); MS (APCI), $(M + 1)^+ = 266$. ^{1}H NMR ($CDCl_3$) δ 7.25 (s, 1 H), 7.00 (d, J = 7.1 Hz, 1 H), 6.94 (s, 1 H), 3.68 (t, J = 7.6, 7.3 Hz, 2 H), 3.52 (br s, 2 H), 3.00 (t, J = 7.3, 7.3 Hz, 2 H), 2.57 (s, 2 H), 2.27 (s, 3 H), 0.99 (s, 6 H).

EXAMPLE 62

1-{6-{2-[4-(1H-Indazol-3-yl)-piperazin-1-yl]-ethyl}-3,3-dimethyl-3,4-dihydro-2H-quinolin-1-yl)-ethanone

A mixture of 3-piperazin-1-yl-1H-indazole hydrochloride (520 mg, 2.60 mmol), 1-[6-(2-chloroethyl)-3,3-dimethyl-3,4-dihydro-2H-quinolin-1-yl]-ethanone (791 mg, 2.98 mmol), anhydrous potassium carbonate (791 mg, 5.70 mmol) and potassium iodide (75 mg) in acetonitrile (50 ml) was refluxed for 72 hours. The reaction mixture was concentrated and the residue was partitioned between water and methylene chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude product was eluted through a flash column (silica gel 60, 230-400 mesh, 5% MeOH in EtOAc) and taken up in methylene chloride. Treatment with 4.0 N HCl solution in dioxane precipitated the dihydrochloride salt. Yield = 496 mg (38%); Anal. calculated for $C_{26}H_{33}N_5O$•2HCl: C, 61.90; H, 6.99; N, 13.88. Found: C, 61.50: H, 7.27; N, 13.45. MS (APCI), $(M + 1)^+ = 432$; $(M - 1)^+ = 430$. ^{1}H-NMR (DMSO-d_6) δ 12.18 (s, 1 H), 10.75 (br s, 1 H), 7.75 (d, J = 8.3 Hz, 1 H), 7.34 (m, 3 H), 7.02 (m, 3 H), 3.92 (br d, H = 10.5 Hz, 2 H), 3.61-3.22 (m, 10 H), 3.00 (m, 2 H), 2.46 (s, 2 H), 2.16 (s, 3 H), 0.89 (s, 6 H).

EXAMPLE 63

1-{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-ethanone; compound with methanesulfonic acid

A. 7-Chloro-6-(2-chloroethyl)-4,4-dimethyl-3,4-dihydro-1*H*-quinolin-2-one

Triethylsilane (10.0 mL, 62.6 mmol) was added to a stirred solution of 7-chloro-6-(2-chloroacetyl)-4,4-dimethyl-3,4-dihydro-1H-quinolin-2-one (5.03 g, 17.6 mmol) in trifluoroacetic acid (25 mL) at 0 °C under nitrogen (N_2). After stirring for 5 min, the cooling bath was replaced with a heating bath, and the thermostat set for 50 °C. After stirring for 15 hours (h), the mixture was allowed to cool, poured into H_2O (150 mL), then extracted twice with EtOAc (150 mL). The extracts were combined, washed with H_2O (150 mL), saturated $NaHCO_3$, and saturated sodium chloride (NaCl), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel (100 g), eluting with 800 mL of 10% EtOAc/hexanes to remove the triethylsilane (Et_3SiH) (collected as a single fraction), then eluting with 1.5 L of 40% EtOAc/hexanes to elute the product) to give the title compound (1.93 g, 40%) as an off-white amorphous solid. Due to the low mass recovery, the initial column wash was examined and determined to contain more of the product. The initial column wash was concentrated *in vacuo* to give a mixture of solid and liquid. The liquid was decanted, and the solid washed and decanted twice with hexanes. The solid was dried under vacuum to give more of the title compound (1.82 g, 38%) as an off-white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (br s, 1 H), 7.17 (s, 1 H), 6.84 (s, 1 H), 3.72 (t, J = 7.3 Hz, 2 H), 3.15 (t, J = 7.3 Hz, 2 H), 2.49 (s, 2 H), 1.32 (s, 6 H); ESI MS *m/z* 272 $[C_{13}H_{15}Cl_2NO + H]^+$.

B. 7-Chloro-6-(2-chloroethyl)-4,4-dimethyl-1,2,3,4-tetrahydroquinoline

Borane (25 mL, 38 mmol, 1.5 M in THF) was added portionwise over 5 min to a stirred solution from step A (1.93 g, 7.09 mmol) in anhydrous THF (40 mL) under N_2. The mixture was heated to reflux for 3 h, then allowed to cool. The mixture was quenched by adding (slowly at first) 6 *M* HCl (25 mL) with stirring. The mixture was heated to reflux for 30 min, then allowed to cool. The mixture was diluted with H_2O (100 mL), then NaOH pellets were added until the mixture was strongly alkaline. The organic phase was separated, and the aqueous phase extracted twice with chloroform ($CHCl_3$) (75 mL). The organic phases were combined, dried over

Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel (100 g), 10% EtOAc/hexanes) to give the title compound (1.92 g, 1.83 g theoretical) as a clear, light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (s, 1 H), 6.46 (s, 1 H), 3.92 (br s, 1 H), 3.65 (t, J = 7.7 Hz, 2 H), 3.27–3.32 (m, 2 H), 3.04 (t, J = 7.7 Hz, 2 H), 1.68–1.73 (m, 2 H), 1.27 (s, 6 H); ESI MS *m/z* 258 $[C_{13}H_{17}Cl_2N + H]^+$.

C. 1-[7-Chloro-6-(2-chloroethyl)-4,4-dimethyl-3,4-dihydro-2*H*-quinolin-1-yl]ethanone

Acetic anhydride (1.0 mL, 11 mmol) was added to a stirred solution from step B (918 mg, 3.56 mmol) and Et_3N (1.5 mL, 11 mmol) in anhyd CH_2Cl_2 (10 mL) under N_2. After stirring for 23 h, MeOH (1 mL) was added to quench the excess reagent. After stirring for 1.25 h, the solvents were removed *in vacuo*. The residue was purified by column chromatography (silica gel (50 g), 10–30% EtOAc/hexanes) to give the title compound (934 mg, 87% from the product of step A) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (br s, 1 H), 7.20 (s, 1 H), 3.79 (t, J = 6.4 Hz, 2 H), 3.73 (t, J = 7.3 Hz, 2 H), 3.16 (t, J = 7.3 Hz, 2 H), 2.27 (s, 3 H), 1.77 (t, J = 6.3 Hz, 2 H), 1.29 (s, 6 H); ESI MS *m/z* 300 $[C_{15}H_{19}Cl_2NO + H]^+$.

D. 1-{6-[2-(4-Benzo[*d*]isoxazol-3-ylpiperazin-1-yl)ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2*H*-quinolin-1-yl}ethanone methanesulfonate

Anhydrous acetonitrile (15 mL) was added to a flask containing the title compound from step C (929 mg, 3.09 mmol), 3-piperazin-1-yl-benzo[*d*]isoxazole hydrochloride (821 mg, 3.43 mmol), potassium carbonate (K_2CO_3) (883 mg, 6.39 mmol), and sodium iodide (NaI) (486 mg, 3.24 mmol) under N_2. The mixture was stirred, giving a suspension. The mixture was heated to reflux overnight (16 h). TLC analysis indicated low conversion, so tetrabutylammonium iodide (Bu_4NI) (3.34 g, 9.04 mmol) was added and the mixture heated to reflux for 4 d, then allowed to cool. TLC analysis indicated moderate conversion. The mixture was diluted with EtOAc (200 mL), then washed twice with H_2O (200 mL) and saturated (saturated) NaCl (75 mL). The combined aqueous phases were reextracted with EtOAc (100 mL), and the extract was washed with H_2O (100 mL) and saturated NaCl (50 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel (50 g), 30–

50% EtOAc/hexanes containing 1% Et_3N) to give the title compound as a free base (945 mg, 65%) as a colorless sticky oil. The product was dissolved in EtOAc (20 mL), then CH_3SO_3H (120 µL, 1.85 mmol) was added dropwise with stirring to give a clear solution. After stirring a couple more minutes, a white precipitate began to form. After stirring for 2 h, the precipitate was collected by suction filtration washing with EtOAc, then dried in a vacuum oven at 50 °C for 20 h to give the title compound (772 mg, 68%) as a white amorphous solid: mp 174–177 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 9.95 (br s, 1 H), 8.08 (d, J = 8.1 Hz, 1 H), 7.75 (br s, 1 H), 7.60–7.68 (m, 2 H), 7.44 (s, 1 H), 7.31–7.41 (m, 1 H), 4.21 (br d, J = 10.8 Hz, 2 H), 3.68–3.79 (m, 4 H), 3.27–3.50 (m + H_2O), 3.09–3.19 (m, 2 H), 2.34 (s, 3 H), 2.22 (s, 3 H), 1.70–1.78 (m, 2 H), 1.26 (s, 6 H); ESI MS *m/z* 467 $[C_{26}H_{31}ClN_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 13.71 min. Anal. Calc'd for $C_{26}H_{31}ClN_4O_2 \cdot CH_3SO_3H$: C, 57.59; H, 6.26; N, 9.95. Found: C, 57.68; H, 6.20; N, 9.74.

EXAMPLE 64

1-{6-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2H-quinolin-1-yl}-2-methyl-propan-1-one; compound with methanesulfonic acid

A. 1-[7-Chloro-6-(2-chloroethyl)-4,4-dimethyl-3,4-dihydro-2*H*-quinolin-1-yl]-2-methylpropan-1-one

Isobutyric anhydride (1.7 mL, 10 mmol) was added to a stirred solution of the title compound of step B of Example 63 (1.00 g, 3.87 mmol) and triethylamine (Et_3N) (2.0 mL, 14 mmol) in anhydrous CH_2Cl_2 (10 mL) under N_2. After stirring for 13 h, TLC analysis indicated only starting material, so the acylation catalyst 4-dimethylaminopyridine (353 mg, 2.89 mmol) was added. After stirring for 17 h, TLC and HPLC analysis indicated low (15%) conversion. The mixture was heated to reflux overnight (21 h), at which point HPLC analysis indicated 50% conversion. The mixture was heated to reflux for another 3 days, during which time most of the solvent evaporated, then allowed to cool. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The organic phase was washed with 0.5 *M* HCl (100 mL), H_2O (100 mL), saturated $NaHCO_3$ (50 mL), and saturated NaCl (50 mL). The aqueous phase was reextracted with EtOAc (100 mL) and the extract washed

as before. (Note: All the extractions and washings were slowed by emulsions.) The organic phases were combined, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel (50 g), 5–15% EtOAc/hexanes) to give the title compound (298 mg, 23%) as a dark yellow, viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (br s, 1 H), 7.21 (s, 1 H), 3.78 (t, J = 6.3 Hz, 2 H), 3.73 (t, J = 7.3 Hz, 2 H), 3.16 (t, J = 7.3 Hz, 2 H), 3.06–3.17 (m, 1 H), 1.76 (t, J = 6.3 Hz, 2 H), 1.29 (s, 6 H), 1.21 (d, J = 7.0 Hz, 3 H), 1.17 (d, J = 6.7 Hz, 3 H); ESI MS *m/z* 328 $[C_{17}H_{23}Cl_2NO + H]^+$.

B. <u>1-{6-[2-(4-Benzo[*d*]isoxazol-3-ylpiperazin-1-yl)ethyl]-7-chloro-4,4-dimethyl-3,4-dihydro-2*H*-quinolin-1-yl}-2-methylpropan-1-one methanesulfonate</u>

Anhydrous acetonitrile (10 mL) was added to a flask containing the product from step A (293 mg, 0.893 mmol), 3-piperazin-1-yl-benzo[*d*]isoxazole hydrochloride (243 mg, 1.01 mmol), K_2CO_3 (271 mg, 1.96 mmol), and sodium iodide (NaI) (459 mg, 3.06 mmol) under N_2. The mixture was stirred to give a suspension, then heated to reflux. After 2 d at reflux, HPLC analyses indicated approximately 50% conversion. More anhydrous acetonitrile (10 mL) was added to replace solvent that had escaped, then the mixture was heated to reflux overnight (23 h). HPLC analysis indicated approximately 1:2 SM/Pdt. After heating to reflux overnight (total reaction time = 4 d), the mixture was allowed to cool. HPLC analysis indicated approximately 1:3 SM/Pdt. The mixture was diluted with EtOAc, washed twice with H_2O, once with saturated NaCl, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography (silica gel (18 g), 30–50% EtOAc/hexanes containing 1% Et_3N) to give the free base of the title compound (234 mg, 53%) as a dark yellow oil. The product was dissolved in EtOAc (10 mL), then methanesulfonic acid (CH_3SO_3H) (30 μL, 1.0 equiv.) was added dropwise with stirring. After stirring for 5 min, hexanes (5 mL) was added to the stirred solution. After stirring another 5 min, a precipitate began to form. After stirring for 2 h, the precipitate was collected by suction filtration washing with EtOAc, then dried in a vacuum oven at 50°C for 22 h to give the title compound (134 mg, 48%) as a light brown amorphous solid: mp 153–157 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.91

(br s, 1 H), 8.08 (d, J = 8.1 Hz, 1 H), 7.56–7.68 (m, 3 H), 7.45 (s, 1 H), 7.33–7.39 (m, 1 H), 4.12–4.27 (m, 2 H), 3.69–3.80 (m, 4 H), 3.24–3.48 (m + H_2O), 3.02–3.19 (m, 2 H), 2.32 (s, 3 H), 1.69–1.77 (m, 2 H), 1.27 (s, 6 H), 1.06 (d, J = 6.6 Hz, 6 H); ESI MS m/z 495 $[C_{28}H_{35}ClN_4O_2 + H]^+$; HPLC >99% (AUC), t_R = 15.37 min. Anal. Calc'd for $C_{28}H_{35}ClN_4O_2 \cdot CH_3SO_3H$: C, 58.92; H, 6.65; N, 9.48. Found: C, 58.92; H, 6.76; N, 9.33.

EXAMPLE 65

1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[b]azepin-1-yl}-ethanone; compound with methanesulfonic acid

A. 7-(2-Chloro-ethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine

A solution of 7-(2-chloroethyl)-1,3,4,5-tetrahydro-benzo[b]azepin-2-one (784 mg, 3.50 mmol) (Example 36 of US Patent No. 5,350,747) in THF (15 mL) was added dropwise to a solution of BH_3 in THF (15.0 mL, 1.5 M, 22.5 mmol). The mixture was heated to reflux for 3 h, then allowed to cool. The reaction was quenched with 6N HCl until gas evolution subsided. The mixture was heated to reflux for 1 h, allowed to cool, and then made basic with solid NaOH. The biphasic mixture was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 9:1 hexanes/EtOAc) to give the title compound (0.55 g, 75%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 1.9 Hz, 1 H), 6.88 (dd, J = 7.8, 2.1 Hz, 1 H), 6.68 (d, J = 7.8 Hz, 1 H), 3.76 (bs, 1 H), 3.66 (t, J = 7.7 Hz, 2 H), 3.01-3.04 (m, 2 H), 2.96 (t, J = 7.7 Hz, 2 H), 2.72-2.76 (m, 2 H), 1.75-1.83 (m, 2 H), 1.59-1.67 (m, 2 H); ESI MS m/z 210 $[C_{12}H_{16}ClN + H]^+$; R_f 0.62 (silica gel, 2:1 hexanes/EtOAc).

B. 1-[7-(2-Chloro-ethyl)-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl]-ethanone

A solution of the title compound from step A (0.55 g, 2.6 mmol) in CH_2Cl_2 (20 mL) was treated with acetic anhydride (Ac_2O) (0.25 mL, 2.6 mmol). After stirring at rt under N_2 for 7.5 h, the reaction was quenched with saturated sodium bicarbonate ($NaHCO_3$) (50 mL) and extracted with CH_2Cl_2 (4 x 50 mL). The combined organic layers were dried over Na_2SO_4, decanted, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:1

hexanes/EtOAc) to give the title compound (602 mg, 91%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1 H), 7.08 (s, 2 H), 4.66-4.71 (m, 1 H), 3.73 (t, J = 7.3 Hz, 2 H), 3.06 (t, J = 7.3 Hz, 2 H), 2.58-2.76 (m, 3 H), 1.79-1.97 (m, 3 H), 1.86 (s, 3 H), 1.30-1.45 (m, 1 H); ESI MS *m/z* 252 $[C_{14}H_{18}ClNO + H]^+$; R_f 0.30 (silica gel, 2:1 hexanes/EtOAc).

C. **1-{7-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3,4,5-tetrahydro-benzo[*b*]azepin-1-yl}-ethanone methanesulfonate**

A solution of the title compound from step B (602 mg, 2.39 mmol) in CH_3CN (20 mL) was treated with 3-piperazin-1-yl-benzo[*d*]isothiazole • HCl (683 mg, 2.67 mmol), NaI (406 mg, 2.71 mmol), and K_2CO_3 (1.09 g, 7.86 mmol). The mixture was heated to reflux under N_2 for 43 h, then allowed to cool. The mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, decanted, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (silica gel, EtOAc) to give a white solid residue (430 mg, 0.99 mmol, 41%). The residue was dissolved in EtOAc (10 mL) and treated with a solution of CH_3SO_3H in Et_2O (0.5 mL, 2M, 1 mmol). After stirring for 5 min, the resulting precipitate was isolated by filtration, washed with Et_2O (3 x 10 mL), and dried in a vacuum oven at 50 °C for 3 d to give the title compound (465 mg, 89%) as a white powder: mp 189-190 °C (dec); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.76 (s, 1 H), 7.85 (t, J = 7.8 Hz, 2 H), 7.51-7.56 (m, 1 H), 7.39-7.45 (m, 1 H), 7.14-7.18 (m, 2 H), 7.08 (d, J = 7.8 Hz, 1 H), 4.66-4.70 (m, 1 H), 4.11-4.20 (m, 2 H), 3.95-4.03 (m, 2 H), 3.68 (d, J = 11.3 Hz, 2 H), 3.13-3.34 (m, 6 H), 2.91 (s, 3 H), 2.68-2.78 (m, 2 H), 2.51-2.59 (m, 1 H), 1.74-2.00 (m, 3 H), 1.83 (s, 3 H), 1.32-1.40 (m, 1 H); ESI MS *m/z* 435 $[C_{25}H_{30}N_4OS + H]^+$; R_f 0.35 (silica gel, 95:5 EtOAc/MeOH); HPLC) >99% (AUC), t_R = 12.68 min. Anal. Calc'd for $C_{25}H_{30}N_4OS•CH_3SO_3H$: C, 58.84; H, 6.46; N, 10.56. Found: C, 58.56; H, 6.49; N, 10.31.

PREPARATION 32

5-(3-Chloro-propionyl)-3,3-dimethyl-1,3-dihydro-indol-2-one

The title compound was prepared using a procedure similar to that described in Preparation 28 using chloro propionyl chloride as the acylating agent. Yield = 3.05 g (98%); MS (APCI), $(M + 1)^+$ = 252.

PREPARATION 33

5-(3-Chloro-propyl)-3,3-dimethyl-1,3-dihydro-indol-2-one

The title compound was prepared using a procedure similar to that described in Preparation 29. Yield = 2.87g (100%); MS (APCI), $(M + 1)^+ = 238$.

PREPARATION 34

5-(3-Chloro-propyl)-3,3-dimethyl-2,3-dihydro-1H-indole

The title compound was prepared using a procedure similar to that described in Preparation 30. Yield = 0.172g (7%); MS (APCI), $(M + 1)^+ = 224$.

PREPARATION 35

1-[5-(3-Chloro-propyl)-3,3-dimethyl-2,3-dihydro-indol-1-yl]-ethanone

A solution of 5-(3-chloro-propyl)-3,3-dimethyl-2,3-dihydro-1H-indole (172 mg) in THF (2.0 mL) with triethylamine (0.145 mL) was treated with acetic anhydride (0.145 mL) and stirred for 14 hours at reflux. The reaction was quenched with water, extracted with ethyl acetate and filter and concentrated *in vacuo*. Yield: 159 mg (78%) MS (APCI), $(M+1)^+ = 266$.

EXAMPLE 66

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-3,3-dimethyl-2,3-dihydro-indol-1-yl}-ethanone

To a stirring solution of 1-[5-(3-chloro-propyl)-3,3-dimethyl-2,3-dihydro-indol-1-yl]-ethanone (159 mg) in acetonitrile (20 mL) was added 3-piperazin-1-yl-benzo[*d*]isothiazole (263 mg), potassium carbonate (332 mg) and water (20 mL) the reaction was warmed to reflux for 72 hours. The reaction cooled and precipitate was filtered off. Yield: 114 mg (45%) MS (APCI), $(M+1)^+ = 449.1$.

PREPARATION 36

2,3-Dihydro-1*H*-isoindole

Beilstein Registry Number 111921; CAS Registry Number 496-12-8

PREPARATION 37

1-(1,3-dihydroisoindol-2-yl)ethanone

Beilstein Registry Number 131840; CAS Registry Number 18913-38-7

PREPARATION 38

1-(2-Acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-2-chloroethanone

Anhydrous CS_2 (15 mL) and chloroacetyl chloride (0.75 mL, 9.4 mmol) were added to a stirred (mechanical stirrer) mixture of the title compound of Preparation 37 (1.00 g, 6.20 mmol) and $AlCl_3$ (3.3 g, 4.0 mmol) under N_2. The mixture was heated to reflux for 3 h, then allowed to cool, to give a dark oil with very little CS_2 remaining over it due to evaporation/leakage. Some ice was added to the stirred oil to quench the excess reagent. After stirring for 5 min, 6 M HCl (25 mL) was added. After stirring for 1 h, the solid precipitate was collected by suction filtration washing with water, then dried in vacuo at 55 °C for 15 h to give the title compound (1.19 g, 81%) as a brown amorphous solid: ^{1}H NMR (500 MHz, C_6D_6; low solubility, but this solvent gave the best spectral dispersion of the aromatic signals; Note: The spectrum shows two sets of signals due to rotational isomers) δ 7.58 (d, J = 7.7 Hz, 0.5 H), 7.37 (s, 0.5 H), 7.29 (d, J = 7.9 Hz, 0.5 H), 7.25 (s, 0.5 H), 6.55 (d, J = 7.9 Hz, 1 H), 4.53 (br s, 2 H), 3.91 (s, 1 H), 3.89 (s, 1 H), 3.65 (br s, 2 H), 1.654 (s, 1.5 H), 1.646 (s, 1.5 H); ^{1}H NMR (300 MHz, $CDCl_3$; Note: The spectrum shows two sets of signals due to rotational isomers) δ 7.88–7.95 (m, 2 H), 7.44 (d, J = 8.6 Hz, 0.5 H), 7.40 (d, J = 8.0 Hz, 0.5 H), 4.88 (br s, 2 H), 4.86 (br s, 2 H), 4.71 (s, 1 H), 4.70 (s, 1 H), 2.20 (s, 1.5 H), 2.19 (s, 1.5 H); Variable Temperature ^{1}H NMR (500 MHz, DMSO-d_6) spectra at 25°C and 90°C showed differences consistent with rotational isomerization; ESI MS *m/z* 238 $[C_{12}H_{12}ClNO_2 + H]^+$; HPLC 98.5% (AUC), t_R = 13.09 min.

EXAMPLE 67

1-(2-Acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-2-(4-benzo[*d*]isothiazol-3-ylpiperazin-1-yl)ethanone

A mixture (suspension) of the title compound of Preparation 38 (2.10 g, 8.84 mmol), 3-piperazin-1-yl-benzo[*d*]isothiazole hydrochloride (2.49 g, 9.72 mmol), K_2CO_3 (3.63

g, 26.3 mmol), and NaI (1.40 g, 9.34 mmol) in anhyd CH_3CN (90 mL) under N_2 was stirred at 25 °C for 20 h, then the solvent was removed in vacuo. The residue was suspended in H_2O, then extracted twice with EtOAc, however a solid remained undissolved in the aqueous phase. The solid was collected by suction filtration, washing and triturating with H_2O, then dried in a vacuum oven at 50°C for 3 d to give the title compound (2.68 g, 72%) as a light brown amorphous solid. Both TLC and ^1H NMR analyses indicated that the product was of high purity: ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.1 Hz, 1 H), 7.98 (br s, 1 H), 7.90 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 1 H), 7.32–7.43 (m, 2 H), 4.87 (br s, 2 H), 4.85 (br s, 2 H), 3.91 (s, 1 H), 3.90 (s, 1 H), 3.59–3.67 (m, 4 H), 2.81–2.89 (m, 4 H), 2.20 (s, 1.5 H), 2.19 (s, 1.5 H); ESI MS *m/z* 421 $[C_{23}H_{24}N_4O_2S + H]^+$.

EXAMPLE 68

1-(2-Acetyl-2,3-dihydro-1*H*-isoindol-5-yl)-2-(4-benzo[*d*]isoxazol-3-ylpiperazin-1-yl)ethanone

The title compound was prepared from the title compound of Preparation 38 (2.18 g, 9.17 mmol) and 3-piperazin-1-yl-benzo[*d*]isoxazole hydrochloride (2.40 g, 10.0 mmol) by the procedure used to prepare the title compound of Example 67 (3.03 g, 82%) as an off-white amorphous solid: ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 8.1 Hz, 1 H), 7.95 (br s, 1 H), 7.69 (d, J = 8.1 Hz, 1 H), 7.35–7.53 (m, 3 H), 7.18–7.26 (m, 1 H), 4.87 (br s, 2 H), 4.85 (br s, 2 H), 3.91 (s, 1 H), 3.90 (s, 1 H), 3.62–3.70 (m, 4 H), 2.80–2.87 (m, 4 H), 2.20 (s, 1.5 H), 2.19 (s, 1.5H); ESI MS *m/z* 405 $[C_{23}H_{24}N_4O_3 + H]^+$.

EXAMPLE 69

1-{5-[2-(4-Benzo[*d*]isothiazol-3-ylpiperazin-1-yl)-1-hydroxyethyl]-1,3-dihydroisoindol-2-yl}ethanone

Sodium borohydride (0.20 g, 5.3 mmol) was added to a stirred solution of the title compound of Example 67 (2.67 g, 6.35 mmol) in 1:1 MeOH/$CHCl_3$ (130 mL) at 0°C. The mixture was allowed to warm to rt while stirring overnight. The solvents were removed in vacuo, and the residue was partitioned between $CHCl_3$ (200 mL) and H_2O (100 mL). The aqueous phase was reextracted with $CHCl_3$ (50 mL). The

combined organic phases were washed with saturated NaCl (50 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title compound (2.92 g crude; 2.68 g theoretical) as a light brown amorphous solid (foam): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 1 H), 7.22–7.41 (m, 4 H), 4.77–4.87 (m, 5 H), 4.05 (d, J = 1.9 Hz, 1 H), 3.54–3.69 (m, 4 H), 2.96–3.06 (m, 2 H), 2.49–2.77 (m, 4 H), 2.18 (s, 3 H); ESI MS *m/z* 423 $[C_{23}H_{26}N_4O_2S + H]^+$.

EXAMPLE 70

1-{5-[2-(4-Benzo[*d*]isoxazol-3-ylpiperazin-1-yl)-1-hydroxyethyl]-1,3-dihydroisoindol-2-yl}ethanone

The title compound was prepared from the title compound of Example 68 (2.97 g, 7.34 mmol) using the procedure used to prepare the title compound of Example 69 (3.18 g crude; 2.98 g theoretical) as a light brown amorphous solid (foam): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 1 H), 7.44–7.54 (m, 2 H), 7.20–7.38 (m, 4 H), 4.77–4.87 (m, 5 H), 3.96 (br s, 1 H), 3.58–3.72 (m, 4 H), 2.92–3.02 (m, 2 H), 2.48–2.74 (m, 4 H), 2.18 (s, 3 H); ESI MS *m/z* 407 $[C_{23}H_{26}N_4O_3 + H]^+$.

EXAMPLE 71

1-{5-[2-(4-Benzo[*d*]isothiazol-3-ylpiperazin-1-yl)-1-chloroethyl]-1,3-dihydroisoindol-2-yl}ethanone

Methanesulfonyl chloride (0.80 mL, 10 mmol) was added to a stirred solution of the title compound of Example 69 (2.92 g crude, 6.35 mmol theoretical) and triethylamine (2.0 mL, 14 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0°C under N_2. After stirring for 10 min, the ice-water bath was removed. After stirring for 2 h, TLC analysis indicated that no starting material was remaining. The solution was washed twice with H_2O, once with saturated NaCl, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title compound (2.75 g, 98% from the ketone product of Example 102) as a light brown amorphous solid (foam): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 1 H), 7.22–7.39 (m, 4 H), 5.02 (t, J = 7.0 Hz, 1 H), 4.77–4.85 (m, 4 H), 3.47–3.53 (m,

4 H), 3.13 (ddd, J = 13.5, 7.4, 1.5 Hz, 1 H), 2.94 (dd, J = 13.5, 6.8 Hz, 1 H), 2.66–2.82 (m, 4 H), 2.180 (s, 1.5 H), 2.178 (s, 1.5 H); ESI MS *m/z* 441 [$C_{23}H_{25}ClN_4OS$ + H]$^+$.

EXAMPLE 72

1-{5-[2-(4-Benzo[*d*]isoxazol-3-ylpiperazin-1-yl)-1-chloroethyl]-1,3-dihydroisoindol-2-yl}ethanone

The title compound was prepared from the title compound of Example 70 (3.18 g crude, 7.34 mmol theoretical) using the procedure used to prepare the title compound of Example 71 (2.96 g, 95% from the ketone product of Example 103) as a light brown amorphous solid (foam): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 1 H), 7.41–7.52 (m, 2 H), 7.17–7.38 (m, 4 H), 5.01 (t, J = 7.0 Hz, 1 H), 4.78–4.86 (m, 4 H), 3.49–3.58 (m, 4 H), 3.10 (ddd, J = 13.5, 7.4, 1.4 Hz, 1 H), 2.93 (dd, J = 13.5, 6.6 Hz, 1 H), 2.63–2.80 (m, 4 H), 2.18 (s, 3 H); ESI MS *m/z* 425 [$C_{23}H_{25}ClN_4O_2$ + H]$^+$.

EXAMPLE 73

1-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-ethanone methanesulfonate

A stirred solution of the title compound of Example 71 (2.74 g, 6.21 mmol) and tributyl tin hydride (Bu_3SnH) (2.5 mL, 9.3 mmol) in anhydrous toluene (170 mL) was degassed by bubbling argon through the solution for 30 min. 2,2'-Azobisisobutyronitrile (AIBN) (0.15 g, 0.91 mmol) was added and the flask was heated with a preheated 80 °C oil bath for 1 h. After allowing to cool, H_2O (10 mL) was added. After stirring for 20 min, the solvents were removed *in vacuo*. The residue was dissolved in $CHCl_3$ (250 mL), then washed with H_2O (100 mL) and saturated NaCl (50 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel (100 g), 1:1:98 MeOH/Et_3N/$CHCl_3$) to give the free base of the title compound (1.28 g, 51%; plus slightly impure fractions: 0.69 g, 27%). The free base was dissolved in warm EtOAc-MeOH, then CH_3SO_3H (0.20 mL, 3.1 mmol, 1.0 equiv.) was added dropwise with stirring. After stirring for 15 min, the solution was diluted with hexanes to

precipitate the salt, which was collected by suction filtration washing with hexanes, then dried overnight (18 h) in a vacuum oven at 50 °C to give the title compound (1.36 g, 87% yield for salt formation, 44% yield from the title compound of Example 71) as a light brown amorphous solid: mp 219–222 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.81 (br s, 1 H), 8.16 (d, J = 8.2 Hz, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.61 (t, J = 7.2 Hz, 1 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.22–7.38 (m, 3 H), 4.81 (br s, 2 H), 4.60 (br d, J = 5.3 Hz, 2 H), 4.14 (br d, J = 9.2 Hz, 2 H), 3.68–3.75 (m, 2 H), 3.02–3.12 (m, 2 H), 2.34 (s, 3 H), 2.072 (s, 1.5 H), 2.066 (s, 1.5 H); IR (KBr) 3437, 2959, 2920, 1643, 1448, 1423, 1207, 1035, 973, 774, 558 cm^{-1}; ESI MS *m/z* 407 $[C_{23}H_{26}N_4OS + H]^+$; HPLC 95.7% (AUC), t_R = 11.78 min. Anal. Calc'd for $C_{23}H_{26}N_4OS•CH_3SO_3H•0.1\ CH_3OH•0.25\ H_2O$: C, 56.81; H, 6.07; N, 11.03. Found: C, 56.65; H, 6.22; N, 10.71.

EXAMPLE 74

1-{5-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-ethanone methanesulfonate

The title compound was prepared from the title compound of Example 72 (2.95 g, 6.94 mmol) using the procedure used to prepare the title compound of Example 73 (1.44 g, 43%) as a white amorphous solid: mp 217–220 °C dec; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.87 (br s, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 7.59–7.67 (m, 2 H), 7.22–7.39 (m, 4 H), 4.81 (br s, 2 H), 4.60 (br d, J = 4.8 Hz, 2 H), 4.19 (br d, J = 11.5 Hz, 2 H), 3.71 (br d, J = 10.3 Hz, 2 H), 3.01–3.11 (m, 2 H), 2.34 (s, 3 H), 2.07 (s, 1.5 H), 2.06 (s, 1.5 H); IR (KBr) 3438, 1631, 1529, 1449, 1198, 1058 cm^{-1}; ESI MS *m/z* 391 $[C_{23}H_{26}N_4O_2 + H]^+$; HPLC 96.3% (AUC), t_R = 11.16 min. Anal. Calc'd for $C_{23}H_{26}N_4O_2•CH_3SO_3H•0.1\ CH_3OH•H_2O$: C, 57.00; H, 6.43; N, 11.03. Found: C, 57.17; H, 6.49; N, 10.92.

PREPARATION 39

3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole

The free base of Example 74, 1-{5-[2-(4-Benzo[*d*]isothiazol-3-ylpiperazin-1-yl)ethyl]-1,3-dihydro-isoindol-2-yl} ethanone, (6.6 g, 1.60 mmol) was dissolved in 630 mL of EtOH and 630 mL of conc. HCl and refluxed for 77 h. After reaction, the solvent was

removed to afford the title compound (7.4 g) as a light brown solid. m.p.: 112-121 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.12-7.93 (dd, 2 H), 7.60-7.40 (m, 5 H), 4.60 (d, 4 H), 4.20 (d, 2 H), 3.80 (d, 2 H), 3.62-3.40 (m, 6 H), 3.30-3.20 (m, 2 H). MS *m/z* 365 [M+1].

EXAMPLE 75

{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-acetic acid methyl ester

To a solution of the title compound from Preparation 39 (4.0 g, 0.91 mmol) in 200 mL of chloroform were slowly added methyl bromoacetate (1.67 g, 1.09 mmol) and triethylamine (7.6 mL, 5.47 mmol). The reaction mixture was stirred at rt overnight, washed with water, dried over sodium sulphate and concentrated. The crude residue was subjected to chromatography (silica gel, EtOAc/MeOH/Et_3N, 98/1/1) to afford the title compound (2.5 g, 63%) as yellow oil, which darkens in the air. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.79 (dd, 2 H), 7.50-7.32 (dt, 2 H), 7.16-7.04 (m, 3 H), 4.08 (s, 4 H), 3.78 (s, 2 H), 3.62-3.58 (m, 6 H), 2.88-2.60 (m, 8 H). MS *m/z* 437 [M+1].

EXAMPLE 76

{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-acetic acid

A solution of the title compound from Example 75 (2.5 g, 0.57 mmol) in THF/H_2O (100/10 mL) was treated with $LiOH·H_2O$ (0.36 g, 0.86 mmol). The reaction mixture was stirred at rt overnight. The solvent was removed under reduced pressure. The crude product was diluted with water, and neutralized with 0.5 N HCl to pH = 7. The solution was extracted with DCM, dried over sodium sulphate and concentrated to give the title compound (2.49 g) as green solid. The crude product is pure in NMR spectrum, but is 75 % purity in HPLC analysis. The title compound was further purified by chromatography (silica gel, MeOH/CH_2Cl_2/acetic acid, 40/60/0.1). Yellow oil was obtained, but it darkens quickly. It is 85 % purity in HPLC analysis. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.95-7.79 (dd, 2 H), 7.50-7.30 (dt, 2 H), 7.16-7.10 (m, 3 H), 4.70-4.50 (br s, 4 H), 3.80 (s, 2 H), 3.62-3.58 (br s, 4 H), 2.90-2.60 (m, 8 H). MS *m/z* 423 [M+1].

EXAMPLE 77

2-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-1-[3-dimethylamino-pyrrolidin-1-yl]-ethanone

Oxalyl chloride (0.42 g, 3.30 mmol) was added dropwise to a stirred solution of the title compound from Example 76 (0.70 g, 1.65 mmol) and DMF (2 drops) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the residue was suspended in CH_2Cl_2 (15 mL), which was added dropwise to a stirred solution of 3-(dimethylamino)pyrrolidine (0.28 g, 2.47 mmol) and triethylamine (1.8 mL, 13.25 mmol). The reaction mixture was stirred at rt for 3 h, 100 mL of CH_2Cl_2 was added. The solution was washed with water, dried over sodium sulphate and concentrated. The crude residue was subjected to chromatography ($MeOH/CH_2Cl_2/Et_3N$, 2/98/0.5) to provide the title compound (0.27 g, 31 %) as a light brown oil, which was treated with 4 mL of 2M solution of hydrogen chloride in ether to provide the title compound as hydrochloride salt. mp 181-188 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.90-11.50 (m, 3 H), 8.10 (m, 2 H), 7.60-7.23 (m, 5 H), 4.90 (m, 2 H), 4.60 (m, 4 H), 4.10 (d, 2 H), 4.00-3.00 (m, 15 H), 2.72 (br s, 6 H), 2.40-2.20 (m, 2 H). MS m/z 519 [M+1]. Anal. Calcd for $C_{29}H_{38}N_6OS \cdot 3HCl \cdot 4H_2O$: C, 49.75; H, 7.05; N, 12.00. Found: C, 49.06; H, 6.32; N, 11.01.

EXAMPLE 78

2-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-N-(2-dimethylamino-ethyl)-N-methyl-acetamide

Oxalyl chloride (0.42 g, 3.30 mmol) was added dropwise to a stirred solution of the title compound from Example 76 (0.70 g, 1.65 mmol) and DMF (2 drops) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at rt for 3 h. The solvent was removed under reduced pressure and the residue was suspended in CH_2Cl_2 (15 mL), which was added dropwise to a stirred solution of amine (0.25 g, 2.47 mmol) and triethylamine (1.8 mL, 13.25 mmol). The reaction mixture was stirred at rt for 3 h, 100 mL of CH_2Cl_2 was added. The solution was washed with water, dried over

sodium sulphate and concentrated. The crude residue was subjected to chromatography (MeOH/ CH_2Cl_2/Et_3N, 2/98/0.5) to provide the title compound (0.28 g, 34 %) as a light brown oil, which was treated with 4 mL of 2 M solution of hydrogen chloride in ether to provide the title compound as hydrochloride salt. mp 152-160 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.79 (br s, 1 H), 11.35 (br s, 1 H), 10.86 (br s, 1 H), 8.15 (m, 2 H), 7.62-7.28 (m, 5 H), 5.00-4.30 (m, 10 H), 4.10 (d, 2 H), 3.80-3.10 (m, 11 H), 2.99 (s, 2 H), 2.75 (d, 6 H). MS m/z 507 [M+1]. Anal. Calcd for $C_{27}H_{36}N_6OS•3HCl•5H_2O$: C, 47.62; H, 7.28; N, 11.90. Found: C, 47.28; H, 6.86; N, 11.06.

PREPARATION 40

N-chloroacetyl-morpholine

To a solution of chloroacetyl chloride (2.0 mL, 2.5 mmol) in 20 mL CH_2Cl_2 was slowly added a solution of morpholine (2.2 mL, 5.0 mmol) in 20 mL CH_2Cl_2 at -78 °C. The reaction mixture was warmed to rt and stirred for 3 h. A white suspension solution resulted. The white precipitate was filtered off. The filtrate was washed with 1 N HCl, dried over sodium sulphate and concentrated to give the title compound (3.11 g, 78 %) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 2 H), 3.74 (br s, 4 H), 3.61 (br s, 2 H), 3.50 (br s, 2 H). MS *m/z* 164 [M+1].

EXAMPLE 79

2-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-1 morpholin-4-yl-ethanone

A mixture of the title compound from Preparation 39 (0.40 g, 0.091 mmol), the title compound from Preparation 40 (0.15 g, 0.092 mmol), potassium carbonate (0.38 g, 0.28 mmol) and sodium iodide (0.15 g, 0.10 mmol) was suspended in 40 mL of acetonitrile and stirred under reflux overnight, cooled to rt, solvent was removed, and water was added. The mixture was extracted with CH_2Cl_2, dried over sodium sulphate and concentrated. The crude residue was subjected to chromatography (MeOH/CH_2Cl_2/acetic acid, 3/97/0.1) to provide the title compound (0.27 g, 60 %) as light yellow oil, which darken quickly in the air. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93-7.80 (dd, 2 H), 7.50-7.37 (dt, 2 H), 7.12-7.06 (m 3 H), 4.01 (s, 4 H), 3.71-3.58 (m 14

H), 2.90-2.65 (m, 8 H). MS *m/z* 292 [M+1]. Anal. Calcd for $C_{27}H_{33}N_5O_2S \cdot 1.5H_2O$: C, 62.52; H, 7.00; N, 13.50. Found: C, 62.63; H, 6.48; N, 13.03.

EXAMPLE 80

2-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl} N-(2-methoxy-ethyl)-acetamide hydrochloride

A mixture of the title compound from Preparation 39 (1.00 g, 2.28 mmol), 2-chloro-1-(methoxyethylamino)ethanone (0.34 g, 2.28 mmol), potassium carbonate (0.94 g, 6.84 mmol) and sodium iodide (0.37 g, 2.50 mmol) was suspended in 100 mL of acetonitrile and stirred under reflux overnight, cooled to rt. The solvent was removed, and water was added. The mixture was extracted with CH_2Cl_2, dried over sodium sulphate and concentrated. The crude residue was subjected to chromatography ($MeOH/CH_2Cl_2$, 3/97) to provide the title compound (0.53 g, 49 %) as a light brown oil, which was treated with 4 mL of 2 M solution of hydrogen chloride in ether to provide the title compound as a hydrochloride salt. mp 149-154 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.70 (br s, 1 H), 11.40 (br s, 1 H), 8.68 (br s, 1 H), 8.13 (m, 2 H), 7.62-7.20 (m, 5 H), 4.90-4.80 (m, 2 H), 4.50 (br s, 2 H), 4.13 (br s, 2 H), 4.10 (d, 2 H), 3.65-3.43 (m, 4 H), 3.46-3.05 (m, 13 H). MS *m/z* 480 [M+1]. Anal. Calcd for $C_{26}H_{33}N_5O_2S \cdot 2HCl \cdot 2H_2O$: C, 53.06; H, 6.68; N, 11.90. Found: C, 53.01; H, 5.80; N, 11.34.

PREPARATION 41

Morpholin-4-yl-acetic acid methyl ester

To a solution of morpholine (5.46 mL, 39.2 mmol) and triethylamine (1.71 mL, 19.6 mmol) in THF (100 mL), methyl bromoacetate (1.86 mL, 19.6 mmol) was added. The reaction mixture was stirred at rt for 5 h. The solvent was removed under reduced pressure. Sodium bicarbonate solution was added. The mixture was extracted with EtOAc, dried over sodium sulphate and concentrated to provide the title compound (2.7 g, 87 %) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (t, 4 H), 3.73 (s, 3 H), 3.23 (s, 2 H), 2.58 (t, 4 H). MS *m/z* 160 [M+1].

PREPARATION 42

Morpholin-4-yl-acetic acid lithium salt

A mixture of morpholin-4-yl-acetic acid methyl ester (2.7 g, 16.9 mmol) and lithium hydroxide (1.06g, 2.54 mmol) in THF (100 mL) and water (10 mL) was stirred at rt overnight. Light yellow solution resulted. The solvent was removed under reduced pressure to provide the title compound (3.6 g, quant.) as a lithium salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.62 (t, 4 H), 3.13 (s, 2 H), 2.62 (t, 4 H). MS *m/z* 146 [M+1].

EXAMPLE 81

1-{5-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-1,3-dihydroisoindol-2-yl}-2-morpholin-4-yl-ethanone

A mixture of the title compound of Preparation 39, 3-{4-[2-(2,3-dihydro-1H-isoindol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole dichloride (0.50 g, 1.14 mmol), the product of Preparation 42 (0.30g, 1.37 mmol), HBTU (0.86 g, 2.28 mmol), HOBt (0.31 g, 2.28 mmol) and diisopropylethylamine (1.0 mL, 6.84 mmol) in 7 mL of DMF was stirred at rt under argon overnight, 200 mL of EtOAc was added. The solution was washed with water (4 x 100 mL). The organic layer was concentrated. The crude residue was subjected to chromatography (MeOH/CH_2Cl_2/EtOAc/Et_3N, 1/20/20/0.1) to provide the title compound (0.12 g, 23 %) as a light yellow oil, which was treated with 4 mL of 2M solution of hydrogen chloride in ether to provide the title compound as hydrochloride salt. mp 183-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (br s, 1 H), 10.42 (br s, 1 H), 8.15 (m, 2 H), 7.60 (m, 1 H), 7.45 (m, 1 H), 7.40-7.28 (m, 3 H), 4.83-4.70 (dd, 4 H), 4.39 (br s, 2 H), 4.10 (d, 2 H), 4.00-3.15 (m, 18 H). MS *m/z* 492 [M+1]. Anal. Calcd for $C_{27}H_{33}N_5O_2S$•2HCl•3H_2O: C, 52.42; H, 6.68; N, 11.32. Found: C, 52.84; H, 6.36; N, 10.96.

EXAMPLE 82

3-{4-[2-(2-Methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole hydrochloride

3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (0.55 g, 1.25 mmol) and triethylamine (0.35 ml, 2.50 mmol) were

dissolved in 10 mL of CH_2Cl_2 at 0°C. Methanesulfonyl chloride (0.17 g, 1.50 mmol) was added slowly. The reaction mixture was warmed to rt and stirred for 2 h, 50 mL of CH_2Cl_2 was added. The solution was washed with water, dried over sodium sulphate and concentrated. The crude residue was subjected to chromatography (MeOH/CH_2Cl_2, 2/98) to provide the title compound (0.32 g, 58 %) as a light yellow oil, which was treated with 5 mL of 2 M solution of hydrogen chloride in ether to provide the title compound as hydrochloride salt. mp 179 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.00 (br s, 1 H), 8.10 (m, 2 H), 7.62 (dt, 1 H), 7.45 (dt, 1 H), 7.30 (m, 3 H), 4.60 (br s, 4 H), 4.10 (d, 2 H), 3.61 (d, 2 H), 3.59-3.10 (m, 8 H), 2.98 (s, 3 H). MS *m/z* 443 [M+1]. Anal. Calcd for $C_{22}H_{26}N_4O_2S_2$•HCl: C, 55.16; H, 5.68; N, 11.69. Found: C, 54.52; H, 5.43; N, 11.13.

EXAMPLE 83

1-{5-[3-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydroisoindol-2-yl}-ethanone

A. 2,3-Dihydro-1*H*-isoindole

Beilstein Registry Number 111921; CAS Registry Number 496-12-8

B. 1-(1,3-dihydroisoindol-2-yl)ethanone

Beilstein Registry Number 131840; CAS Registry Number 18913-38-7

C. 1-(2-Acetyl-2,3-dihydro-1H-isoindol-5-yl)-3-chloro-propan-1-one

Anhydrous CS_2 (15 mL) and chloropropionyl chloride (0.81 mL, 9.4 mmol) were added to a stirred (mechanical stirrer) mixture of the product of step B (1.00 g, 6.20 mmol) and $AlCl_3$ (3.3 g, 4.0 mmol) under N_2. The mixture was heated to reflux for 3 h, then allowed to cool, to give a dark oil with very little CS_2 remaining over it due to evaporation/leakage. Some ice was added to the stirred oil to quench the excess reagent. After stirring for 5 min, 6M HCl (25 mL) was added. After stirring for 1 h, the solid precipitate was collected by suction filtration washing with water, then dried in vacuo at 55 °C for 15 h to give the title product (1.29 g, 83%) as a brown solid: ESI MS *m/z* 251 [M+1] ; HPLC (Method A) 98.5% (AUC), t_R = 13.27 min.

D. 1-(2-Acetyl-2,3-dihydro-1H-isoindol-5-yl)-3-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-propan-1-one

A mixture (suspension) of 1-(2-Acetyl-2,3-dihydro-1H-isoindol-5-yl)-3-chloro-propan-1-one (2.14 g, 8.84 mmol), 3-piperazin-1-yl-benzo[*d*]isothiazole hydrochloride (2.49

g, 9.72 mmol), K_2CO_3 (3.63 g, 26.3 mmol), and NaI (1.40 g, 9.34 mmol) in anhydrous CH_3CN (90 mL) under N_2 was stirred at 25 °C for 20 h, then the solvent was removed *in vacuo*. The residue was suspended in H_2O, then extracted twice with EtOAc, however a solid remained undissolved in the aqueous phase. The solid was collected by suction filtration, washing and triturating with H_2O, then dried in a vacuum oven at 50 °C for 3 d to give the titled product (2.74 g, 71%) as a light brown amorphous solid. ESI MS *m/z* 435 [M+1].

E. 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-1-hydroxy-propyl]-1,3-dihydro-isoindol-2-yl}-ethanone

Sodium borohydride (0.20 g, 5.3 mmol) was added to a stirred solution of the product of step D (2.69 g, 6.35 mmol) in 1:1 MeOH/$CHCl_3$ (130 mL) at 0 °C. The mixture was allowed to warm to room temperature while stirring overnight. The solvents were removed *in vacuo*, and the residue was partitioned between $CHCl_3$ (200 mL) and H_2O (100 mL). The aqueous phase was reextracted with $CHCl_3$ (50 mL). The combined organic phases were washed with sat'd NaCl (50 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title product (2.7 g) as a light brown solid: ESI MS *m/z* 437 [M+1].

F. 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-1-chloro-propyl]-1,3-dihydro-isoindol-2-yl}-ethanone

Methanesulfonyl chloride (0.80 mL, 10 mmol) was added to a stirred solution of the product of step E (2.7 g, 6.35 mmol) and triethylamine (2.0 mL, 14 mmol) in anhydrous CH_2Cl_2 (200 mL) at 0 °C under N_2. After stirring for 10 min, the ice-water bath was removed. After stirring for 2 h, TLC analysis indicated that no starting material was remaining. The solution was washed twice with H_2O, once with saturated NaCl, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the title product (2.75 g) as a light brown solid: ESI MS *m/z* 455 [M+1].

G. 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-ethanone

A stirred solution of the product of step F (2.74 g, 6.21 mmol) and Bu_3SnH (2.5 mL, 9.3 mmol) in anhyrous toluene (170 mL) was degassed by bubbling argon through the solution for 30 min. AIBN (0.15 g, 0.91 mmol) was added and the flask was heated with a preheated 80 °C oil bath for 1 h. After allowing to cool, H_2O (10 mL) was added. After stirring for 20 min, the solvents were removed *in vacuo*. The

residue was dissolved in $CHCl_3$ (250 mL), then washed with H_2O (100 mL) and saturated NaCl (50 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The residue was purified by column chromatography (silica gel (100 g), 1:1:98 MeOH/Et_3N/$CHCl_3$) to give the free base of the title compound (2.1 g, 87%) as a light brown solid: ESI MS *m/z* 421 [M+1].

H. 3-{4-[3-(2,3-Dihydro-1H-Isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole

The product of step G (6.6 g, 1.60 mmol) was dissolved in 630 mL of EtOH and 630 mL of conc. HCl and refluxed for 77 h. After reaction, the solvent was removed to afford 3-{4-[3-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (7.4 g) as a light brown solid. MS *m/z* 379 [M+1].

I. 1-{5-[3-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydroisoindol-2-yl}-ethanone

Acetic anhydride (0.62 mL, 6.6 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (1.0 g, 2.6 mmol), triethylamine (1.62 mL, 11.6 mmol), 4-dimethylamino- pyridine (0.08 g, 0.65 mmol), and anhydrous dichloromethane (40 mL) at rt. The reaction mixture was stirred overnight at rt. The resulting solution was washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue thus obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using ethyl acetate:methanol:acetic acid (88:10:2) solvent mixture as eluent to obtain the acetylated amine product. The product was dissolved in 40 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (5.0 mL, 5 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (2 x 10 mL), and dried under vacuum. Yield: 0.884 g, 73.2 %. mp 130.0 – 133.0 °C. HPLC: Purity 98.10% (retention time: 9.918 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^1H NMR (400 MHz, DMSO-d_6): δ10.9 (br s, 1 H), 7.88 (d, 1 H), 7.83 (d, 1 H), 7.48 (t, 1 H), 7.36 (t, 1 H), 7.21 (t, 1 H), 7.14 (m, 2 H), 4.79 (m, 4 H), 3.67 (m, 4 H), 2.89 (m, 4 H), 2.67 (t, 2 H), 2.63 (t, 2 H), 2.18 (s, 3 H), 1.93 (t, 2 H). ES-MS m/z 420.58 $(C_{24}H_{28}N_4OS + 1)^+$. Analysis calculated for $C_{24}H_{28}N_4OS$•HCl: C, 63.07; H, 6.40; N, 12.26. Found C, 63.03; H, 6.51; N, 12.08.

EXAMPLE 84

{5-[3-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydroisoindol-2-yl}-acetic acid

Step A:

Methyl bromoacetate (0.28 mL, 2.9 mmol) was added to a suspension containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (1.0 g, 2.6 mmol), potassium carbonate (0.44 g, 3.2 mmol) and anhydrous acetonitrile (50 mL) at rt and stirred overnight. Solvent was evaporated and the residue was distributed between chloroform (50 mL) and water (30 mL). The organic layer was separated, dried over Na_2SO_4, and evaporated. The residue was purified over silica gel column (230 - 400 mesh, 2.5 x 18 cm) using methanol:ethyl acetate (1.5:98.5) solvent mixture as eluent to obtain pure {5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-acetic acid methyl ester. Yield: 0.12 g, 10.08%. Using triethylamine as a base, the yield was improved to 67.8%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, 1 H), 7.80 (d, 1 H), 7.47 (t, 1 H), 7.36 (t, 1 H), 7.11 (d, 1 H), 7.08 (d, 1 H), 4.09 (s, 4 H), 3.76 (s, 2 H), 3.62 (s, 3 H), 3.56 (m, 4 H), 2.67 (m, 4 H), 2.64 (m, 2 H), 2.44 (t, 2 H), 1.85 (m, 2 H). ES-MS m/z 451.08 $(C_{25}H_{30}N_4O_2S + 1)^+$.

Step B:

Lithium hydroxide monohydrate (0.1 g, 2.4 mmol) was added to a solution containing {5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-acetic acid methyl ester (0.6 g, 1.3 mmol), tetrahydrofuran (30 mL), and water (4 mL), and stirred overnight. The solution was evaporated to dryness and the residue was dissolved in 3 mL of water, and pH was adjusted to 6 using 1 M HCl. The resulting solution was evaporated to dryness, and washed with ether (2 x 10 mL) and tetrahydrofuran (2 x 10 mL). As the elemental analysis results were not satisfactory, the product was further purified using HP20 Diaion column (Supelco product). The impure product was treated with 1 mL of triethylamine and then loaded over HP20 column. After washing the column with methanol:water (1:1), elution with acetonitrile yielded pure product containing fractions, which were evaporated, and dried under vacuum. Yield: 0.44 g, 72.7 %. m.p. 78.0 – 80.0 °C. HPLC: Purity 94.45% (retention time: 11.601 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, 1 H), 7.79 (d,

2 H), 7.46 (t, 1 H), 7.37 (t, 1 H), 7.13 (m, 2 H), 7.07 (s, 1 H), 4.58 (s, 4 H), 3.77 (s, 2 H), 3.58 (m, 4 H), 2.70 (m, 4 H), 2.67 (m, 2 H), 2.47 (m, 2 H), 1.86 (m, 2 H). ES-MS m/z 437.09 $(C_{24}H_{28}N_4O_2S + 1)^+$. Analysis calculated for $C_{24}H_{28}N_4O_2S.\bullet 0.5Et_3N\bullet H_2O$: C, 64.19; H, 7.50; ,N 12.48. Found: C, 65.26; H, 6.94; N, 12.41.

EXAMPLE 85

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-dimethylamino-ethanone

Chloroacetylchloride (0.15 mL, 1.9 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.5 g, 1.1 mmol), 4-dimethylaminopyridine (0.014 g, 0.01 mmol), triethylamine (0.7 mL, 5.0 mmol) and dichloromethane (50 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the absence of starting material and formation of 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. The resultant solution was washed with $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to obtain crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. This was dissolved in acetonitrile (50 mL), and to which was added dimethylamine (1.11 mL of 2 M MeOH solution, 2.2 mmol), potassium carbonate (0.18 g, 1.3 mmol), and sodium bromide (0.028 g, 0.30 mmol) at rt, and stirred overnight. The resulting suspension was filtered and the precipitate was washed with chloroform. The filtrate was evaporated, and the residue obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using triethylamine:ethyl acetate:methanol (1:94:5) solvent mixture as eluent to obtain the title compound. The product was dissolved in 5 mL of anhydrous diethylether and to which was added 1 M hydrogen chloride solution in ether (2.0 mL, 2.0 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (3 x 15 mL), and dried under vacuum. Yield: 0.40 g, 66.9 %. mp 90.0 °C turned brown. HPLC: Purity 97.59% (retention time: 11.683 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.62 (br s, 1 H), 10.02 (br s, 1 H), 8.12 (m, 2 H), 7.60 (M, 1 H), 7.49 (m, 1 H), 7.36 (m, 1 H), 7.32 (m, 1 H), 7.23 (m, 1 H), 4.81

(m, 2 H), 4.73 (m, 2 H), 4.33 (s, 2 H), 4.05 (m, 2 H), 3.57 (m, 4 H), 3.30 (m, 2 H), 3.15 (m, 2 H), 2.88 (s, 6 H), 2.72 (m, 2 H), 2.11 (m, 2 H). ES-MS m/z 464.18 $(C_{26}H_{33}N_5OS + 1)^+$. Analysis calculated for $C_{26}H_{33}N_5OS \bullet 2HCl \bullet H_2O$: C, 56.31; H, 6.72; N, 12.63. Found: C, 56.25; H, 6.70; N, 12.32.

EXAMPLE 86

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-piperidin-1-yl-ethanone

Chloroacetylchloride (0.15 mL, 1.9 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.6 g, 1.6 mmol), 4-dimethylaminopyridine (0.020 g, 0.02 mmol), triethylamine (0.97 mL, 6.9 mmol) and acetonitrile (40 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the absence of starting material and formation of 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. Solvent was evaporated to afford an oil, which was diluted with 50 mL of chloroform, washed with $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to obtain crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. This was dissolved in acetonitrile (50 mL), and to which was added piperidine (0.33 mL, 3.3 mmol), potassium carbonate (0.26 g, 1.9 mmol), and sodium bromide (0.040 g, 0.39 mmol) at rt, and stirred overnight. The resulting suspension was filtered and the precipitate was washed with chloroform. The filtrate was evaporated, and the residue obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using triethylamine:ethyl acetate:methanol (1:93:6) solvent mixture as eluent to obtain the title compound. The product was dissolved in 5 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (2.1 mL, 2.1 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (3 x 5 mL), and dried under vacuum. Yield: 0.39 g, 43.6 %. mp 98.0 °C turned brown. HPLC: Purity 94.40% (retention time: 11.987 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^1H NMR (400 MHz, DMSO): δ 11.58 (br s, 1 H), 9.78 (br s, 1 H), 8.12 (m, 2 H), 7.60 (m, 1 H), 7.49 (m, 1 H), 7.36 (m, 1 H), 7.30 (m, 1 H), 7.25 (m, 1 H), 4.83

(m, 2 H), 4.72 (m, 2 H), 4.31 (s, 2 H), 4.02 (m, 4 H), 3.60 (m, 4 H), 3.47 (m, 2 H), 3.30 (m, 2 H), 3.19 (m, 2 H), 3.15 (m, 2 H), 2.70 (br s, 2 H), 2.11 (br s, 2 H), 1.81 (br s, 2 H), 1.68 (br s, 2 H). ES-MS m/z 504.17 $(C_{29}H_{37}N_5OS + 1)^+$. Analysis calculated for $C_{29}H_{37}N_5OS \cdot 2HCl \cdot 0.5H_2O$: C, 59.47; H, 6.90; N, 11.96. Found: C, 59.64; H, 6.89; N, 11.49.

EXAMPLE 87

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-morpholin-4-yl-ethanone

Chloroacetylchloride (0.14 mL, 1.7 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.6 g, 1.6 mmol), potassium carbonate (0.26 g, 1.9 mmol), 4-dimethylaminopyridine (0.050 g, 0.04 mmol), and acetonitrile (40 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the absence of starting material and formation of compound 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. To the same pot was added morpholine (0.28 mL, 3.2 mmol), potassium carbonate (0.4 g, 2.9 mmol), and sodium bromide (0.048 g, 0.47 mmol) at rt, and stirred overnight. The resulting suspension was diluted with 100 mL of chloroform, washed with brine, dried over Na_2SO_4, and evaporated. The residue thus obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 14 cm), using ethyl acetate:methanol:acetic acid (88:10:2) solvent mixture as eluent to obtain the title compound. The product was dissolved in 20 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (5.0 mL, 5 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (2 x 10 mL), and dried under vacuum. Yield: 0.66 g, 71.9 %. mp 179.0 – 183.0 °C. HPLC: Purity 94.29% (retention time: 11.665 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.58 (br s, 1 H), 10.58 (br s, 1 H), 8.12 (m, 2 H), 7.62 (m, 1 H), 7.48 (m, 1 H), 7.30 (m, 3 H), 4.83 (m, 2 H), 4.72 (m, 2 H), 4.42 (s, 2 H), 4.03 (m, 4 H), 3.84 (m, 2 H), 3.6 (m, 4 H), 3.54 (m, 2 H), 3.30 (m, 4 H), 3.16 (m, 2 H), 2.70 (m, 2 H), 2.11 (m, 2 H).

ES-MS m/z 379.08 $(C_{28}H_{35}N_5O_2S + 1)^+$. Analysis calculated for $C_{28}H_{35}N_5O_2S \cdot 2HCl$: C, 58.12; H, 6.45; N, 12.10. Found: C, 58.18; H, 6.51; N, 11.84.

EXAMPLE 88

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-[(2-dimethylamino-ethyl)-methyl-amino]-ethanone

Chloroacetylchloride (0.23 mL, 2.9 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (1.0 g, 2.2 mmol), 4-dimethylaminopyridine (0.010 g, 0.002 mmol), triethylamine (1.4 mL, 9.9 mmol) and dichloromethane (50 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the absence of starting material and formation of 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. The resultant solution was washed with $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to obtain crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. About half of the crude1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone was dissolved in acetonitrile (50 mL), and to which was added *N,N,N*-trimethylethylenediamine (0.29 mL, 2.2 mmol), potassium carbonate (0.18 g, 1.3 mmol), and sodium bromide (0.028 g, 0.27 mmol) at rt, and stirred overnight. The resulting suspension was filtered and the precipitate was washed with chloroform (2 x 10 mL). The filtrate was evaporated and the residue obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 11 cm), using triethylamine:ethyl acetate:methanol (1:94:5) solvent mixture as eluent to obtain the crude title compound. The product was dissolved in 5 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (4.4 mL, 4.4 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (2 x 10 mL), and dried under vacuum. Yield: 0.33 g, 42.9 %. mp 85.1 – 87.3 °C. HPLC: Purity 95.42% (retention time: 11.097 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^1H NMR (400 MHz, DMSO-d_6): δ 11.64 (br s, 1 H), 11.16 (br s, 1 H), 8.14 (m, 2 H), 7.61 (m, 1 H), 7.49 (m, 1 H), 7.36 (m, 1 H), 7.33 (m, 1 H), 7.26 (m, 1 H), 4.84 (m, 2 H), 4.73 (m, 2 H), 4.49 (brs, 2 H), 4.21 (brs, 4 H), 4.05

(m, 2 H), 3.74 (m, 2 H), 3.41 (m, 4 H), 3.28 (m, 2 H), 3.07 (m, 2 H), 2.98 (s, 3 H), 2.85 (s, 6 H), 2.70 (br s, 2H), 2.11 (b.s, 2H). ES-MS m/z 521.26 $(C_{29}H_{40}N_6OS + 1)^+$. Analysis calculated for $C_{29}H_{40}N_6OS \cdot 4HCl \cdot H_2O$: C, 50.88; H, 6.77; N, 12.28. Found: C, 50.50; H, 7.17; N, 11.67.

EXAMPLE 89

1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-diethylamino-ethanone

Chloroacetylchloride (0.23 mL, 2.9 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (1.0 g, 2.2 mmol), 4-dimethylaminopyridine (0.010 g, 0.002 mmol), triethylamine (1.4 mL, 9.9 mmol) and dichloromethane (50 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the absence of starting material and formation of 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. The resultant solution was washed with $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to obtain crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. About half of the crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone was dissolved in acetonitrile (50 mL), and to which was added diethylamine (0.6 mL, 5.7 mmol), potassium carbonate (0.18 g, 1.3 mmol), and sodium bromide (0.025 g, 0.28 mmol) at rt, and stirred overnight. The resulting suspension was filtered and the precipitate was washed with chloroform (2 x 10 mL). The filtrate was evaporated, and the residue obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 11 cm), using triethylamine:ethyl acetate:methanol (1:93:6) solvent mixture as eluent to obtain the title compound. The product was dissolved in 5 mL of anhydrous diethylether and to which was added 1 M hydrogen chloride solution in ether (3.3 mL, 3.3 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (3 x 10 mL), and dried under vacuum. Yield: 0.40 g, 58.3 %. m.p. 90.0 °C turned waxy. HPLC: Purity 95.82% (retention time: 11.936 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^1H NMR (400 MHz, DMSO-d_6): δ 11.76 (br s, 1 H),

9.66 (br s, 1 H), 8.18 (m, 2 H), 7.66 (m, 1 H), 7.55 (m, 1 H), 7.39 (m, 1 H), 7.36 (m, 1 H), 7.31 (m, 1 H), 4.94 (m, 2 H), 4.78 (m, 2 H), 4.36 (s, 2 H), 4.10 (m, 2 H), 3.64 (m, 4 H), 3.36 (m, 4 H), 3.24 (m, 4 H), 2.76 (br s, 2 H), 2.18 (br s, 2rH), 1.29 (m, 6 H). ES-MS m/z 492.22 $(C_{28}H_{37}N_5OS + 1)^+$. Analysis calculated for $C_{28}H_{37}N_5OS \cdot 3HCl \cdot H_2O$: C, 54.32; H, 6.84; N, 11.31. Found: C, 54.45; H, 7.25; N, 11.11.

EXAMPLE 90

{5-[3-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydroisoindol-2-yl}-(3-dimethylamino-pyrrolidin-1-yl)-methanone

Chloroacetylchloride (0.14 mL, 1.7 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.6 g, 1.6 mmol), potassium carbonate (0.26 g, 1.9 mmol), 4-dimethylaminopyridine (0.050 g, 0.04 mmol), and acetonitrile (40 mL) at rt. The reaction mixture was stirred overnight at rt and later an aliquot was examined by NMR, which indicated the presence of starting material. Hence, added triethylamine (1.0 mL, 7.2 mmol) and stirred for an hour. Now, the starting material completely disappeared. The resulting suspension was diluted with 100 mL of chloroform, washed with $NaHCO_3$, brine, dried over Na_2SO_4, and evaporated to obtain crude 1-{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-2-chloro-ethanone. This was dissolved in acetonitrile (50 mL), and to which was added (*S*)-*2*-dimethylaminopyrrolidine (0.36 g, 3.2 mmol), potassium carbonate (0.4 g, 2.9 mmol), and sodium bromide (0.048 g, 0.47 mmol) at rt, and stirred overnight. The resulting suspension was diluted with 100 mL of chloroform, washed with brine, dried over Na_2SO_4, and evaporated. The residue thus obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using chloroform:methanol (88:12) solvent mixture as eluent to obtain the title compound. The product was dissolved in 20 mL of anhydrous tetrahydrofuran and to which was added 1 M hydrogen chloride solution in ether (6.8 mL, 6.8 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (3 x 10 mL), and dried under vacuum. Yield: 0.73 g, 68.8 %. mp 166.0 – 170.0 °C. HPLC: Purity 94.60% (retention time: 11.032 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150

mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.99 (br d, 1 H), 11.66 (br s, 1 H), 11.09 (br s, 1 H), 8.10 (m, 2 H), 7.59 (m, 1 H), 7.47 (m, 1 H), 7.34 (m, 2 H), 7.23 (m, 1 H), 4.82 (br s, 2rH), 4.71 (br s, 2 H), 4.57 (br m, 2 H), 4.43 (br m, 4 H), 4.04 (m, 4 H), 3.72 (m, 2 H), 3.60 (m, 4 H), 3.28 (m, 2 H), 3.14 (m, 2 H), 2.79 (br s, 6 H), 2.40 (br m, 1 H), 2.12 (m, 2 H). ES-MS m/z 533.22 $(C_{30}H_{40}N_6OS + 1)^+$. Analysis calculated for $C_{30}H_{40}N_6OS \cdot 3HCl \cdot 1.5H_2O$: C, 53.84; H, 6.94; N, 12.56. Found: C, 53.84; H, 7.39; N, 11.85.

EXAMPLE 91

5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindole-2-carboxylic acid (4-fluoro-phenyl)-amide

4-Fluorophenylisocyanate (0.15 mL, 1.3 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.5 g, 1.1 mmol), triethylamine (0.46 mL, 3.3 mmol) and tetrahydrofuran (40 mL) at rt. The reaction mixture was stirred for 2 h at rt and later evaporated. The residue was dissolved in 30 mL of dichloromethane, washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated to obtain crude product. Purification over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using triethylamine:ethyl acetate (1:99) solvent mixture as eluent yielded pure title compound. The product was dissolved in 5 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (2.0 mL, 2.0 mmol) with stirring. A white precipitate of hydrogen chloride salt of the title compound was obtained, which was filtered off, washed with ether (3 x 15 mL), and dried under vacuum. Yield: 0.46 g, 75.2 %. mp 145.0 – 150.0 °C. HPLC: Purity 96.34% (retention time: 15.080 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5μm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (br s, 1 H), 8.46 (s, 1 H), 8.10 (m, 2 H), 7.59 (m, 3 H), 7.45 (m, 1 H), 7.30 (m, 1 H), 7.26 (m, 1 H), 7.20 (m, 1 H), 7.12 (m, 2 H), 4.74 (s, 4 H), 4.02 (m, 2 H), 3.56 (m, 2 H), 3.49 (m, 2 H), 3.31 (m, 2 H), 3.16 (m, 2 H), 2.71 (m, 2 H), 2.12 (m, 2 H). ES-MS m/z 516.20 $(C_{29}H_{30}FN_5OS + 1)^+$. Analysis calculated for $C_{29}H_{30}FN_5OS \cdot HCl \cdot 0.5H_2O$: C, 62.07; H, 5.76; N, 12.48. Found: C, 61.83; H, 5.61; N, 12.23.

EXAMPLE 92

5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindole-2-carbothioic acid cyclohexylamide

Cyclohexylisothiocyanate (0.31 mL, 2.2 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.5 g, 1.1 mmol), triethylamine (0.46 mL, 3.3 mmol) and tetrahydrofuran (40 mL) at rt. The reaction mixture was stirred for 2 h at rt and later evaporated. The residue was washed with hexane to remove CyNCS. Purification over silica gel column (230 - 400 mesh, 2.5 x 10 cm) using ethyl acetate as eluent yielded pure title compound as an oil, which was washed with dry ether (2 x 10 mL) to obtain white solid. Yield: 0.35 g, 60.8 %. mp 194.2 – 195.3 °C. HPLC: Purity 98.95% (retention time: 16.571 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (m, 1H), 7.82 (m, 1H), 7.47 (m, 1H), 7.37 (m, 1H), 7.19 (m, 1H), 7.15 (m, 2H), 5.14 (m, 2H), 4.82 (b.s, 2H), 4.37 (m, 1H), 3.58 (b.s, 4H), 2.68 (m, 4H), 2.67 (b.s, 2H), 2.45 (m, 2H), 2.17 (m, 2H), 1.88 (m, 2H), 1.76 (m, 2H), 1.68 (m, 2H), 1.50 (m, 2H), 1.44 (m, 2H), 1.24 (m, 2H). ES-MS m/z 520.20 $(C_{29}H_{37}N_5S_2 + 1)^+$. Analysis calculated for $C_{29}H_{37}N_5S_2$: C, 67.01; H, 7.18; N, 13.47. Found: C, 66.54; H, 7.00; N, 13.18.

EXAMPLE 93

3-{4-[3-(2-Methanesulfonyl-2,3-dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole hydrochloride

Methanesulfonylchloride (0.16 mL, 2.2 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.8 g, 1.8 mmol), triethylamine (4.0 mL, 28.7 mmol) and anhydrous chloroform (50 mL) at 5°C. After 2 h stirring at rt, the reaction mixture was washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated to obtain crude product. Purification over silica gel column (230 - 400 mesh, 2.5 x 12 cm) using ethyl acetate as eluent yielded pure title compound. The product was dissolved in 20 mL of anhydrous tetrahydrofuran and to which was added 1 M hydrogen chloride solution in ether (4.3 mL, 4.3 mmol) with stirring. A white precipitate of hydrogen chloride salt of the title compound was obtained, which was filtered off, washed with ether (3 x 6 mL), and dried under

vacuum. Yield: 0.79 g, 90.4 %. m.p. 201.0- 203.0 °C. HPLC: Purity 97.50% (retention time: 14.072 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.48 (br s, 1 H), 8.14 (m, 1 H), 7.60 (m, 1 H), 7.47 (m, 1 H), 7.29 (m, 1 H), 7.27 (m, 1 H), 7.20 (m, 1 H), 4.61 (s, 4 H), 4.03 (d, 2 H), 3.59 (m, 4 H), 3.30 (m, 2 H), 3.25 (m, 2 H), 2.98 (s, 3 H), 2.69 (m, 2 H), 2.09 (m, 2 H). ES-MS m/z 457.06 $(C_{23}H_{28}N_4O_2S_2 + 1)^+$. Analysis calculated for $C_{23}H_{28}N_4O_2S_2 \bullet HCl \bullet 1.5H_2O$: C, 53.12; H, 6.21; N, 10.78. Found: C, 53.38; H, 5.61; N, 10.33.

EXAMPLE 94

3-{4-[3-(2-Benzenesulfonyl-2,3-dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole hydrochloride

Benzenesulfonylchloride (0.14 mL, 1.06 mmol) was added to a solution containing 3-{4-[2-(2,3-Dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.4 g, 0.88 mmol), triethylamine (0.43 mL, 3.1 mmol) and anhydrous dichloromethane (40 mL) at 5 °C. After 2 h stirring at rt, the reaction mixture was evaporated to obtain a residue, which was washed with hexane (3 x 10 mL), and dried. The residue was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm) using ethyl acetate as eluent to obtain pure title compound. The product was dissolved in 10 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (2.0 mL, 2.0 mmol) with stirring. A white precipitate of hydrogen chloride salt of the title compound was obtained, which was filtered off, washed with ether (3 x 5 mL), and dried under vacuum. Yield: 0.286 g, 62.2 %. mp 130.2 – 133.9 °C. HPLC: Purity 96.92% (retention time: 11.078 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (br s, 1 H), 8.11 (m, 2 H), 7.88 (m, 2 H), 7.69 (m, 1 H), 7.65 (m, 3 H), 7.59 (m, 1 H), 7.45 (m, 1 H), 7.19 (m, 2 H), 4.55 (s, 4 H), 4.05 (d, 2 H), 3.56 (d, 2 H), 3.44 (m, 2 H), 3.26 (m, 2 H), 3.12 (m, 2 H), 2.63 (m, 2 H), 2.02 (m, 2 H). ES-MS m/z 519.23 $(C_{28}H_{30}N_4O_2S_2 + 1)^+$. Analysis calculated for $C_{28}H_{30}N_4O_2S_2 \bullet HCl \bullet H_2O$: C, 58.67; H, 5.80; N, 9.77. Found: C, 58.84; H, 5.54; N, 9.60.

EXAMPLE 95

{5-[3-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-propyl]-1,3-dihydro-isoindol-2-yl}-phenyl-methanone hydrochloride

Benzoic anhydride (0.50 g, 2.2 mmol) was added to a solution containing 3-{4-[2-(2,3-dihydro-1H-isoindol-5-yl)-propyl]-piperazin-1-yl}-benzo[d]isothiazole (0.4 g, 0.88 mmol), triethylamine (0.43 mL, 3.1 mmol), 4-dimethyl-aminopyridine (0.001 g, 0.008 mmol), and anhydrous dichloromethane (40 mL) at rt. The reaction mixture was stirred overnight at rt. The resulting solution was washed with $NaHCO_3$, dried over Na_2SO_4, and evaporated. The residue thus obtained was purified over silica gel column (230 - 400 mesh, 2.5 x 12 cm), using ethyl acetate:methanol solvent mixture (95:5) as eluent to obtain the title product. The product was dissolved in 10 mL of anhydrous ethyl acetate and to which was added 1 M hydrogen chloride solution in ether (2.0 mL, 2 mmol) with stirring. A white precipitate of hydrogen chloride salt was obtained, which was filtered off, washed with ether (2 x 6 mL), and dried under vacuum. Yield: 0.342 g, 74.4 %. mp 120.1 – 123.2 °C. HPLC: Purity 97.45% (retention time: 14.707 min.; mobile phase: 0.1% H_3PO_4/MeCN gradient; column: ACE_C18_5µm_4-6 x 150 mm). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.27 (br s, 1 H), 8.13 (m, 2 H), 7.58 (m, 3 H), 7.49 (m, 4 H), 7.34 (m, 1 H), 7.19 (m, 2 H), 4.84 (m, 2 H), 4.74 (m, 2 H), 4.02 (m, 2 H), 3.86 (br s, 1 H), 3.59 (m, 4 H), 3.15 (m, 4 H), 2.68 (m, 2 H), 2.08 (m, 2 H). ES-MS m/z 482.65 $(C_{29}H_{30}N_4OS + 1)^+$. Analysis calculated for $C_{29}H_{30}N_4OS•HCl•H_2O$: C, 64.85; H, 6.19; N, 10.43. Found: C, 64.39; H, 5.96; N, 10.07.

PREPARATION 43

1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone

To a stirred solution of 1,2,3,4-tetrahydroisoquinoline (10.0 mL, 79.886 mmol) in anhydrous CH_2Cl_2 (200 mL) and pyridine (7.2 mL, 89.021 mmol) under a nitrogen atmosphere was added trifluoroacetic anhydride (12.4 mL, 87.791 mmol). The reaction was stirred overnight at ambient temperature. The reaction was quenched by slow addition of sat. $NaHCO_3$ solution (50 mL) and transferred to a separatory funnel. The layers were separated and the organic layer was extracted with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting

yellow oil was eluted through a flash column (silica gel 60, 230-400 mesh, 0-3% MeOH in CH_2Cl_2 gradient over 1 h) to give a yellow oil. Yield: 17.1459 g (74.808, 94%). MS (APCI), $(M+1)^+ = 230$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 7.15 (m, 2 H), 4.78 (s, 1.3 H), 4.73 (s, 0.7 H), 3.88 (t, *J*=6.0 Hz, 0.7 H), 3.83 (m, 1.3 H), 2.95 (q, *J*=6.0 Hz, 2 H).

PREPARATION 44

1-[7-(2-Chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone

To a stirred solution of 1-(3,4-dihydro-1H-isoquinolin-2-yl)-2,2,2-trifluoro-ethanone (16.7121 g, 72.915 mmol) in anhydrous CH_2Cl_2 (182 mL) was added chloroacetyl chloride (7.0 mL, 87.515 mmol). The reaction was heated to 40 °C (oil bath). Aluminum chloride (38.90 g, 291.735 mmol) was slowly added in portions. The process was slightly exothermic. A reflux condenser was attached and the reaction was heated to reflux. After 2.5 h, the reaction was cooled to ambient temperature and slowly poured into an ice bath and stirred vigorously. The mixture was transferred to a separatory funnel and the aqueous layer extracted with additional CH_2Cl_2. The organic portions were combined and extracted with sat. $NaHCO_3$ solution, passed through a phase separator and then concentrated *in vacuo* to a yellow solid. The solid was eluted through a flash column (silica gel 60, 230-400 mesh, 2% MeOH in CH_2Cl_2) to give an impure yellow solid. The solid was repurified by flash column under the same condition and then recrystallized from EtOAc/hexanes to give pure product as a yellow solid. Yield: 10.5912 g (34.648 mmol, 48%). MS (APCI, $(M-1)^- = 304$. ^1H-NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 2 H), 7.30 (m, 1 H), 4.85 (s, 1.3 H), 4.80 (s, 0.7 H), 4.66 (d, *J*=2.69 Hz, 2 H), 3.89 (m, 2 H), 3.02 (m, 2 H).

PREPARATION 45

1-[7-(2-Chloro-ethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone

To a stirred solution of 1-[7-(2-chloro-acetyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (10.5851 g, 34.628 mmol) in boron trifluoride etherate

(BF_3•Et_2O, 26.4 mL, 0.208 mol) in a sealed tube was added triethylsilane (33.2 mL, 0.208 mol). The tube was sealed and then placed into a preheated 80 °C oil bath. After 4 h, the reaction was cooled to ambient temperature and poured into an ice bath and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. The oil was eluted through a flash column (silica gel 60, 230-400 mesh, 10-25% EtOAc in hexanes gradient over 1 h) to give a brown oil. Yield: 3.5199 g (12.067 mmol, 35%). MS (APCI), $(M+1)^+ = 292$. ^{1}H-NMR (400 MHz, $CDCl_3$,) δ 7.09 (m, 2 H), 6.99 (m, 1 H), 4.77 (s, 1.3 H), 4.72 (s, 0.7 H), 3.85 (m, 2 H), 3.70 (m, 2 H), 3.03 (m, 2 H), 2.93 (m, 2 H).

EXAMPLE 96

1-{7-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl}-2,2,2-trifluoro-ethanone methane sulfonate

A mixture of 3-piperazin-1-yl-benzo[d]isothiazole hydrochloride (0.4056 g, 1.417 mmol), 1-[7-(2-chloro-ethyl)-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (0.3755 g, 1.287 mmol), anhydrous sodium carbonate (0.3019 g, 2.848 mmol) and potassium iodide (0.0259 g, 0.156 mmol) in acetonitrile (10 mL) was allowed to react at 175 °C for 0.5 h in a microwave reactor. The reaction was cooled to ambient temperature. CH_2Cl_2 and H_2O were added and the solution was mixed well then poured into a phase separator. The organic layer was concentrated *in vacuo* to give an oil. The oil was eluted through a flash column (silica gel 60, 230-400 mesh, 30-100% EtOAc in CH_2Cl_2 gradient over 1 h) to give a white waxy/gummy solid. Yield: 0.4106 g (0.865 mmol, 67 %). The solid (0.405 g, 0.853 mmol) was taken up in THF (8.5 mL) and heated to 40 °C. Methanesulfonic acid (55.5 µL, 0.855 mmol) was added and after 5 min, the reaction was allowed to cool to ambient temperature. The product was allowed to crystallize overnight. Hexanes were added to the reaction mixture and the solid was filtered and washed with hexanes. The wet solid was dried in a vacuum oven at 50 °C to give a white/off-white crystalline solid as the mesylate salt. Anal. calculated for $C_{24}H_{25}F_3N_4OS$•CH_4O_3S: C, 52.62; H, 5.12; N, 9.82. Found: C, 52.36, H, 4.98; N, 9.69. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (s, 1

H), 7.84 (d, *J*=7.42 Hz, 2 H), 7.52 (m, 2 H), 7.41 (m, 1 H), 7.12 (m, 2 H), 4.76 (m, 4 H), 4.17 (m, 2 H), 4.00 (m, 4 H), 3.82 (m, 2 H), 3.27 (m, 3 H), 2.91 (m, 6 H).

EXAMPLES 97 AND 98

A. 1,2,3,4-Tetrahydroquinoline

Beilstein Registry Number 116149; CAS Registry Number 635-46-1

B. (3,4-Dihydro-2*H*-quinolin-1-yl)(4-fluorophenyl)methanone

CAS Registry Number 313276-23-2

C. 2-Chloro-1-[1-(4-fluorobenzoyl)-1,2,3,4-tetrahydroquinolin-6-yl]ethanone

Carbon disulfide (100 mL) and chloroacetyl chloride (6.0 mL, 75 mmol) were added sequentially to a mechanically stirred mixture of the compound identified in Step B (13 g crude, 48 mmol theoretical) and $AlCl_3$ (24 g, 180 mmol) under N_2. The mixture was heated to reflux for 3 h, then allowed to cool. After sitting at rt overnight, the clear liquid top phase was decanted (by pipet) off of the dark oil lower phase. Ice water (250 mL) was added cautiously to the stirred dark oil. Then, 6 M HCl (150 mL) was added to the stirred mixture. After stirring for 30 min, the solid was collected by suction filtration washing several times with H_2O. The solid was dried in a vacuum oven at 50 °C for 3 d to give the title compound (14.9 g, 93% from 1,2,3,4-tetrahydroquinoline) as a brown amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 1.8 Hz, 1 H), 7.49 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.37–7.46 (m, 2 H), 6.96–7.06 (m, 2 H), 6.83 (d, *J* = 8.6 Hz, 1 H), 4.63 (s, 2 H), 3.92 (t, *J* = 6.4 Hz, 2 H), 2.93 (t, *J* = 6.6 Hz, 2 H), 2.01–2.13 (m, 2 H); ESI MS *m/z* 332 $[C_{18}H_{15}ClFNO_2 + H]^+$.

D. [6-(2-Chloroethyl)-3,4-dihydro-2*H*-quinolin-1-yl](4-fluorophenyl)methanone

Triethylsilane (7.0 mL, 44 mmol) was added portionwise over 10 min to a stirred solution of the product of Step C (5.03 g, 15.2 mmol) in trifluoroacetic acid (20 mL) under N_2. The mixture was heated to 50 °C for 17 h, then allowed to cool. The mixture (a dark brown solution) was poured into a stirred mixture of 1 M NaOH (300 mL) and ice (100 mL). The two-phase mixture was stirred for 1 h, during which time the dark oil turned into a brown solid. The mixture was extracted with EtOAc (200 mL), which dissolved the brown solid. The organic phase was washed with H_2O (200 mL) and saturated NaCl (100 mL), dried over Na_2SO_4, filtered, and the solvent

was removed *in vacuo*. The residue (brown solid and clear, colorless oil) was purified by column chromatography (silica gel (120 g), 10–40% EtOAc/hexanes) to give the title compound (4.35 g, 90%) as a yellow waxy solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.41 (m, 2 H), 7.01 (br s, 1 H), 6.91–7.00 (m, 2 H), 6.74 (dd, J = 8.2, 1.7 Hz, 1 H), 6.63 (d, J = 8.1 Hz, 1 H), 3.89 (t, J = 6.5 Hz, 2 H), 3.66 (t, J = 7.4 Hz, 2 H), 2.97 (t, J = 7.4 Hz, 2 H), 2.83 (t, J = 6.6 Hz, 2 H), 1.98–2.10 (m, 2 H); ESI MS *m/z* 318 $[C_{18}H_{17}ClFNO + H]^+$.

E. {6-[2-(4-Benzo[*d*]isothiazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2*H*-quinolin-1-yl}-(4-fluorophenyl)-methanone (97)

A stirred mixture of the product of Step D (2.00 g, 6.29 mmol), 3-piperazin-1-yl-benzo[*d*]isothiazole hydrochloride (**9**, 1.82 g, 7.12 mmol), K_2CO_3 (2.34 g, 16.9 mmol), and NaI (1.00 g, 6.67 mmol) in anhyd CH_3CN (60 mL) under N_2 was heated to reflux for 3 d, then allowed to cool. The mixture was diluted with EtOAc (300 mL), then washed twice with H_2O (300 mL), once with saturated NaCl (100 mL), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography (silica gel (150 g), 40–60% EtOAc/hexanes containing 1% Et_3N) to give the title compound (2.75 g, 87%) as a sticky oil and solid mixture. The product was dissolved in warm EtOAc (60 mL), then allowed to cool with stirring. A small amount of precipitate was observed after 30 min. The mixture was diluted with hexanes (120 mL) portionwise over 2 h. After stirring an additional hour, the precipitate was collected by suction filtration washing with hexanes, then dried *in vacuo* at 46 °C for 3 d to give the title compound (1.71 g, 54%) as a white amorphous solid: mp 126–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 1 H), 7.82 (d, J = 8.1 Hz, 1 H), 7.47 (td, J = 7.6, 1.0 Hz, 1 H), 7.32–7.41 (m, 3 H), 7.02 (br s, 1 H), 6.91–7.00 (m, 2 H), 6.76 (dd, J = 8.2, 1.5 Hz, 1 H), 6.60 (br d, J = 7.7 Hz, 1 H), 3.89 (t, J = 6.5 Hz, 2 H), 3.54–3.63 (m, 4 H), 2.60–2.87 (m, 10 H), 2.05 (p, J = 6.6 Hz, 2 H); IR (ATR) 2947, 2835, 1634, 1600, 1504, 1374, 1271, 1227 cm^{-1}; ESI MS *m/z* 501 $[C_{29}H_{29}FN_4OS + H]^+$; HPLC >99% (AUC), t_R = 14.77 min. Anal. calcd. for $C_{29}H_{29}FN_4OS$: C, 69.57; H, 5.84; N, 11.19. Found: C, 69.36; H, 5.86; N, 11.03.

F. **{6-[2-(4-Benzo[*d*]isoxazol-3-yl-piperazin-1-yl)-ethyl]-3,4-dihydro-2*H*-quinolin-1-yl}-(4-fluoro-phenyl)-methanone (98)**

A stirred mixture of the product of Step E (2.30 g, 7.24 mmol), 3-piperazin-1-yl-benzo[*d*]isoxazole hydrochloride (2.03 g, 8.47 mmol), K_2CO_3 (2.66 g, 19.2 mmol), and NaI (1.24 g, 8.27 mmol) in anhyd CH_3CN (75 mL) under N_2 was heated to reflux for 3 d, then allowed to cool. The mixture was diluted with EtOAc (300 mL), then washed twice with H_2O (300 mL). The organic phase was diluted with more EtOAc (200 mL) to dissolve some solid particles, then washed with saturated NaCl (100 mL), dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The residue was dissolved in hot 10% MeOH/EtOAc (220 mL), then allowed to cool with stirring. After stirring for 4 h, no precipitate had formed. The mixture was diluted portionwise with hexanes (200 mL) over the next 2 h to promote precipitation of the product. After stirring overnight, the precipitate was collected by suction filtration washing with 50% EtOAc/hexanes, then hexanes, then dried *in vacuo* at 49 °C for 20 h to give the title compound (1.65 g, 47%) as a white amorphous solid: mp 170–172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1 H), 7.43–7.53 (m, 2 H), 7.33–7.41 (m, 2 H), 7.18–7.26 (m, 1 H), 7.01 (br s, 1 H), 6.96 (t, J = 8.7 Hz, 2 H), 6.75 (dd, J = 8.2, 1.5 Hz, 1 H), 6.60 (br d, J = 7.8 Hz, 1 H), 3.89 (t, J = 6.5 Hz, 2 H), 3.58–3.65 (m, 4 H), 2.58–2.86 (m, 10 H), 2.05 (p, J = 6.5 Hz, 2 H); IR (ATR) 1630, 1602, 1527, 1498, 1445, 1385, 1230 cm^{-1}; ESI MS *m/z* 485 $[C_{29}H_{29}FN_4O_2 + H]^+$; HPLC 98.8% (AUC), t_R = 14.16 min. Anal. calcd. for $C_{29}H_{29}FN_4O_2$: C, 71.88; H, 6.03; N, 11.56. Found: C, 71.75; H, 6.08; N, 11.38.

PREPARATION 46

1-(4-Fluoro-2,3-dihydro-indol-1-yl)-ethanone

A 10 mL flask equipped with a magnetic stir bar was charged with 4-fluoro-1H-indole (1.0g, 7.4 mmol). The solid was dissolved in glacial acetic acid (10mL). Sodium cyanoborohydride (932 mg, 14.8 mmol) was added portion-wise, and the reaction stirred at ambient temperature while being monitored by TLC. After 72 hours, the reaction was quenched by drop-wise addition of H_2O and the pH was adjusted to ~8 with 1N NaOH. The aqueous layer was extracted with CH_2Cl_2 (3x). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated *in*

vacuo. A yellow oil weighing 1.14g was obtained. The yellow oil was dissolved in THF (50 mL). Triethylamine (1.7 mL, 12.5 mmol) was added with stirring, followed by acetyl chloride (688 µL, 9.9 mmol). The reaction stirred overnight for 15 hours and was then quenched by drop-wise addition of H_2O. The aqueous phase was extracted with CH_2Cl_2 (3x), the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 1.58 g of a light yellow solid. The yellow solid was recrystallized from 2-propanol to yield 1-(4-fluoro-2,3-dihydro-indol-1-yl)-ethanone as white needle crystals weighing 858 mg (65%, 2 steps).

PREPARATION 47

1-(1-Acetyl-4-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone

A 50 mL flask was equipped with a magnetic stir bar, charged with 1-(4-fluoro-2,3-dihydro-indol-1-yl)-ethanone (358 mg, 2.0 mmol) and aluminum chloride (400 mg, 3 mmol). The flask was fitted with a nitrogen bubbler, purged with nitrogen gas and cooled to 0 °C in an ice water bath. Chloro-acetyl chloride (242 µL, 3.0 mmol) was added drop-wise to the stirring solution, and the reaction was allowed to gradually warm to ambient temperature. The reaction stirred at rt for two hours, and was then fitted with a condenser and heated to reflux. After an additional two hours, an additional 1.5 equivalents of $AlCl_3$ (400 mg) were added and the reaction stirred overnight at reflux. When all starting material had disappeared by TLC, the reaction was quenched by drop-wise addition of H_2O. The contents of the flask were extracted with CH_2Cl_2 (3x) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 368 mg of a brown solid that was shown to be the desired product (66%).

PREPARATION 48

1-[5-(2-Chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone

A 25 mL flask equipped with a magnetic stir bar was charged with 1-(1-acetyl-4-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone (368 mg, 1.44 mmol), and the contents were dissolved in trifluoroacetic acid (3.2 mL). The flask was fitted with a rubber septum and purged with nitrogen gas. After drop-wise addition of triethylsilane (690 µL, 4.32 mmol), the reaction was heated to 50 °C in an oil bath.

Stirring continued for 4 hours, after which time no starting material was visible by TLC. The contents of the flask were poured into a seperatory funnel containing water and extracted with dichloromethane (3x). The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 334 mg of a brown solid shown to be the desired product (89%).

EXAMPLE 99

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-fluoro-2,3-dihydro-indol-1-yl}-ethanone

A microwave vessel equipped with a magnetic stir bar was charged with 1-[5-(2-chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone (121 mg, 0.5 mmol), 3-piperazin-1-yl-benzo[d]isoxazole (180 mg as the HCl salt, 0.75 mmol), and sodium carbonate (106 mg, 1 mmol). The contents of the vessel were diluted with 2.5 mL H_2O, the vessel was sealed, placed in a CEM Discover microwave, and heated to 175 °C for a duration of 10 minutes. After cooling to rt, the contents were diluted with 2 mL of an 8:1 solution of ethanol:NH_4OH and extracted three times with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield 367 mg of a crude brown solid. The solid was purified on a column of silica gel (15g) using a slow elution gradient of CH_2Cl_2 to 100:8:1 CH_2Cl_2:ethanol:NH_4OH over the course of an hour. The isolated brown solid weighed 148 mg (73%).

EXAMPLE 100

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-fluoro-2,3-dihydro-indol-1-yl}-ethanone

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-fluoro-2,3-dihydro-indol-1-yl}-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone and 3-piperazin-1-yl-benzo[d]isothiazole. Yield: 35 mg (39%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 425.1 $[M+H]^+$.

EXAMPLE 101

1-(4-Fluoro-5-{2-[4-(5-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone

1-(4-Fluoro-5-{2-[4-(5-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone and 5-fluoro-3-piperazin-1-yl-benzo[d]isoxazole. Yield: 50 mg (40%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 427.1 $[M+H]^+$.

PREPARATION 49

1-(4-Chloro-2,3-dihydro-indol-1-yl)-ethanone

1-(4-Chloro-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Preparation 46 for 1-(4-fluoro-2,3-dihydro-indol-1-yl)-ethanone starting with 4-chloroindole yield: 923 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.20 (s, 3 H) 3.18 (t, *J*=8.55 Hz, 2 H) 4.07 (t, *J*=8.55 Hz, 2 H) 6.97 (d, *J*=8.06 Hz, 1 H) 7.11 (d, *J*=8.06 Hz, 1 H) 8.08 (d, *J*=8.06 Hz, 1 H).

PREPARATION 50

1-(1-Acetyl-4-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone

1-(1-Acetyl-4-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone was prepared in a similar fashion as decribed above in Preparation 47 for 1-(1-acetyl-4-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone starting with 1-(4-chloro-2,3-dihydro-indol-1-yl)-ethanone] yield: 180 mg (26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.24 (s, 3 H) 3.25 (t, *J*=8.67 Hz, 2 H) 4.14 (m, 2 H) 4.68 (s, 2 H) 7.57 (d, *J*=8.30 Hz, 1 H) 8.14 (d, *J*=8.30 Hz, 1 H).

PREPARATION 51

1-[4-Chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone

1-[4-Chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone was prepared in a similar fashion as decribed above in Preparation 48 for 1-[5-(2-chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone starting with 1-(1-acetyl-4-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone yield: 168g (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

ppm 2.20 (s, 3 H) 3.17 (m, 4 H) 3.68 (t, *J*=7.45 Hz, 2 H) 4.09 (t, *J*=8.55 Hz, 2 H) 7.09 (d, *J*=8.06 Hz, 1 H) 8.03 (m, *J*=8.06 Hz, 1 H).

EXAMPLE 102

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-4-chloro-2,3-dihydro-indol-1-yl]-ethanone and 3-piperazin-1-yl-benzo[d]isothiazole. Yield: 117 mg (83%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 441.1 $[M+H]^+$.

EXAMPLE 103

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-4-chloro-2,3-dihydro-indol-1-yl}-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-4-chloro-2,3-dihydro-indol-1-yl]-ethanone and 3-piperazin-1-yl-benzo[d]isoxazole. Yield: 75 mg (59%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 425.0 $[M+H]^+$.

PREPARATION 52

1-(6-Fluoro-2,3-dihydro-indol-1-yl)-ethanone

1-(6-Fluoro-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Preparation 46 for 1-(4-fluoro-2,3-dihydro-indol-1-yl)-ethanone starting with 6-fluoroindole yield: 1.85 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.20 (s, 3 H) 3.14 (t, *J*=8.55 Hz, 2 H) 4.08 (m, 2 H) 6.68 (t, *J*=8.55 Hz, 1H) 7.05 (m, 1H) 7.94 (d, *J*=10.75 Hz, 1 H).

PREPARATION 53

1-(1-Acetyl-6-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone

1-(1-Acetyl-6-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone was prepared in a similar fashion as decribed above in Preparation 47 for 1-(1-acetyl-4-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone starting with 1-(6-fluoro-2,3-dihydro-indol-1-yl)-ethanone yield: 665 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 3 H) 3.20 (t, *J*=8.43 Hz, 2 H) 4.15 (t, *J*=8.43 Hz, 2 H) 4.70 (d, *J*=2.93 Hz, 2 H) 7.76 (d, *J*=6.84 Hz, 1 H) 7.97 (d, *J*=13.19 Hz, 1 H).

PREPARATION 54

1-[5-(2-Chloro-ethyl)-6-fluoro-2,3-dihydro-indol-1-yl]-ethanone

1-[5-(2-Chloro-ethyl)-6-fluoro-2,3-dihydro-indol-1-yl]-ethanone was prepared in a similar fashion as decribed above for Preparation 48 starting with 1-(1-acetyl-6-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone yield: 168g (84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.20 (s, 3 H) 3.01 (t, *J*=7.08 Hz, 2 H) 3.14 (t, *J*=8.30 Hz, 2 H) 3.67 (t, *J*=7.08 Hz, 2 H) 4.07 (t, *J*=8.55 Hz, 2 H) 6.98 (d, *J*=7.33 Hz, 1 H) 7.92 (d, *J*=11.72 Hz, 1 H).

EXAMPLE 104

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-6-fluoro-2,3-dihydro-indol-1-yl]-ethanone and 3-piperazin-1-yl-benzo[d]isothiazole. Yield: 146 mg (57%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 425.1 $[M+H]^+$.

EXAMPLE 105

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone

1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-fluoro-2,3-dihydro-indol-1-yl}-ethanone was prepared in a similar fashion as decribed above in Example

99 starting with 1-[5-(2-chloro-ethyl)-6-fluoro-2,3-dihydro-indol-1-yl]-ethanone and 3-piperazin-1-yl-benzo[d]isoxazole. Yield: 123mg (50%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 409.1 $[M+H]^+$.

PREPARATION 55

1-(6-Chloro-2,3-dihydro-indol-1-yl)-ethanone

1-(6-Chloro-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Preparation 46 for 1-(4-fluoro-2,3-dihydro-indol-1-yl)-ethanone starting with 6-chloroindole yield: 2.05 g (80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.10 (s, 3 H) 3.06 (t, J=8.42 Hz, 2 H) 4.06 (m, 2 H) 6.97 (dd, J=7.93, 2.07 Hz, 1 H) 7.18 (d, J=8.05 Hz, 1 H) 7.99 (d, J=2.20 Hz, 1 H).

PREPARATION 56

1-(1-Acetyl-6-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone

1-(1-Acetyl-6-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone was prepared in a similar fashion as decribed above in Preparation 47 for 1-(1-acetyl-4-fluoro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone starting with 1-(6-chloro-2,3-dihydro-indol-1-yl)-ethanone] yield: 2.8 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 3 H) 3.21 (t, J=8.54 Hz, 2 H) 4.14 (t, J=8.54 Hz, 3 H) 4.75 (s, 2 H) 7.49 (s, 1 H) 8.29 (s, 1 H).

PREPARATION 57

1-[6-Chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone

1-[6-Chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone was prepared in a similar fashion as decribed above in Preparation 48 for 1-[5-(2-chloro-ethyl)-4-fluoro-2,3-dihydro-indol-1-yl]-ethanone starting with 1-(1-acetyl-6-chloro-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone yield: 1.87g (96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.10 (s, 3 H) 3.03 (m, 4 H) 3.74 (t, J=7.08 Hz, 2 H) 4.06 (t, J=8.54 Hz, 2 H) 7.22 (s, 1 H) 8.00 (s, 1 H).

EXAMPLE 106

1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone

1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[6-chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone and 6-fluoro-3-piperazin-1-yl-benzo[d]isothiazole. Yield: 47 mg (51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.12 (s, 3 H) 2.52 (m, 2 H) 2.65 (m, 4 H) 2.81 (m, 2 H) 3.07 (m, 2 H) 3.41 (m, 4 H) 4.07 (t, J=8.55 Hz, 2 H) 7.22 (s, 1 H) 7.27 (m, 1 H) 7.93 (m, 1 H) 8.00 (s, 1 H) 8.07 (m, 1 H). Isolated in 97% purity @ 254 nm; LCMS (APCI) 459 $[M+H]^+$.

The following compounds were prepared from 1-[6-chloro-5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone and the appropriate piperazine or piperidine in a fashion similar to that reported above.

EXAMPLE	APPROPRIATE PIPERAZINE OR PIPERDINE	COMPOUND NAME	DATA
#107	5-methoxy-3-piperazin-1-yl-benzo[d]isothiazole	1-(6-Chloro-5-{2-[4-(5-methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 52 mg (55%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 471 $[M+H]^+$.
#108	7-fluoro-3-piperazin-1-yl-benzo[d]isothiazole	1-(6-Chloro-5-{2-[4-(7-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 64 mg (70%), Isolated in 94% purity @ 254 nm; LCMS (APCI) 459 $[M+H]^+$.
#109	7-methoxy-3-piperazin-1-yl-benzo[d]isothiazole.	1-(6-Chloro-5-{2-[4-(7-methoxy-benzo[d]isothiazol-3-yl)-	Yield: 49 mg (52%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 471 $[M+H]^+$.

		piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	
#110	3-piperidin-4-yl-benzo[d]isothiazole	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperidin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	Yield: 54 mg (61%), Isolated in 95% purity @ 254 nm; LCMS (APCI) 440 $[M+H]^+$.
#111	5-fluoro-3-piperazin-1-yl-benzo[d]isothiazole	1-(6-Chloro-5-{2-[4-(5-fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 52 mg (57%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 459 $[M+H]^+$.
#112	6-fluoro-3-piperidin-4-yl-benzo[d]isoxazole	1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperidin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 29 mg (31%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 458 $[M+H]^+$.
#113	3-piperazin-1-yl-benzo[d]isoxazole	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	Yield: 14 mg (16%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 425 $[M+H]^+$.
#114	5-fluoro-3-piperazin-1-yl-benzo[d]isoxazole	1-(6-Chloro-5-{2-[4-(5-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 40 mg (45%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 443 $[M+H]^+$.
#115	5-chloro-3-piperazin-1-yl-benzo[d]isoxazole	1-(6-Chloro-5-{2-[4-(5-chloro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-	Yield: 38 mg (41%), Isolated in 91% purity @ 254 nm; LCMS (APCI) 459 $[M+H]^+$.

		ethyl}-2,3-dihydro-indol-1-yl)-ethanone	
#116	6-fluoro-3-piperazin-1-yl-benzo[d]isoxazole.	1-(6-Chloro-5-{2-[4-(6-fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 40 mg (44%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 443 $[M+H]^+$
#117	6-methyl-3-piperazin-1-yl-benzo[d]isoxazole	1-(6-Chloro-5-{2-[4-(6-methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 40 mg (46%), Isolated in 91% purity @ 254 nm; LCMS (APCI) 439 $[M+H]^+$.
#118	7-methyl-3-piperazin-1-yl-benzo[d]isoxazole	1-(6-Chloro-5-{2-[4-(7-methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 43 mg (49%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 439 $[M+H]^+$.
#119	1-benzo[b]thiophen-3-yl-piperazine	1-{5-[2-(4-Benzo[b]thiophen-3-yl-piperazin-1-yl)-ethyl]-6-chloro-2,3-dihydro-indol-1-yl}-ethanone	Yield: 79 mg (86%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 458 $[M+H]^+$.
#120	3-piperazin-1-yl-1H-indazole	1-(6-Chloro-5-{2-[4-(1H-indazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 35 mg (41%), Isolated in 100% purity @ 254 nm; LCMS (APCI) 424 $[M+H]^+$.

PREPARATION 58

1-(2,3-Dihydro-indol-1-yl)-ethanone

A solution of 11.2 mL (0.1 mol) of indoline (commercially available from Aldrich Chemical company) in THF (200mL) was treated with triethyl amine (15.33 mL, 0.11 mol) followed by dropwise addition of acetyl chloride (7.82 mL, 0.11 mol).

The reaction was stirred at room temperature for 20 hours, quenched with water (50 mL) followed by concentration *in vacuo*. White solid was collected and washed with water. Yield: 15.7 g (97.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.11 (s, 3 H) 3.09 (t, *J*=8.55 Hz, 2 H) 4.03 (m, 2 H) 6.95 (m, 1 H) 7.10 (s, 1 H) 7.19 (d, *J*=6.84 Hz, 1 H) 8.01 (d, *J*=7.82 Hz, 1 H).

PREPARATION 59

1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone

1-(1-Acetyl-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone was prepared in a similar fashion as decribed above in Preparation 47 starting with 1-(2,3-dihydro-indol-1-yl)-ethanone] yield: 11.85 g (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.26 (d, *J*=3.90 Hz, 3 H) 3.25 (t, *J*=8.42 Hz, 2 H) 4.13 (t, *J*=8.54 Hz, 2 H) 4.67 (s, 2 H) 7.80 (m, 2 H) 8.26 (d, *J*=8.30 Hz, 1 H).

PREPARATION 60

1-[5-(2-Chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone

1-[5-(2-Chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone was prepared in a similar fashion as decribed above in Preparation 48 starting with 1-(1-acetyl-2,3-dihydro-1H-indol-5-yl)-2-chloro-ethanone yield: 2.85 g (85%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.11 (s, 3 H) 2.92 (t, *J*=7.08 Hz, 2 H) 3.08 (t, *J*=8.55 Hz, 2 H) 3.76 (t, *J*=7.20 Hz, 2 H) 4.04 (t, *J*=8.55 Hz, 2 H) 7.00 (d, *J*=8.30 Hz, 1 H) 7.11 (s, 1 H) 7.92 (d, *J*=8.30 Hz, 1 H).

EXAMPLE 121

1-(5-{2-[4-(6-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone

1-(5-{2-[4-(6-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone was prepared in a similar fashion as decribed above in Example 99 starting with 1-[5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone and 6-fluoro-3-piperazin-1-yl-benzo[d]isothiazole. The crude products were purified by HPLC (30x100 mm ODS-A C(18) 5u column). Yield: 20 mg (24%). R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6

mm LUNA C_{18}.Isolated in 100% purity @ 254 nm HPLC: R_t = 9.693; MS (APCI), $(M+1)^+$ = 425.1.

The following compounds were prepared from 1-[5-(2-chloro-ethyl)-2,3-dihydro-indol-1-yl]-ethanone and the appropriate piperazine or piperidine in a fashion similar to that reported above. The crude products were purified by HPLC (30x100 mm ODS-A C(18) 5u column).

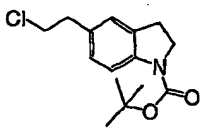
Example	Appropriate Piperazine or Piperidine	Compound Name	Data
#122	5-methoxy-3-piperazin-1-yl-benzo[d]isothiazole	1-(5-{2-[4-(5-Methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 37 mg (42%), Isolated in 95% purity @ 254 nm HPLC: R_t = 16.04; MS (APCI), $(M+1)^+$ = 437.3.
#123	7-fluoro-3-piperazin-1-yl-benzo[d]isothiazole	1-(5-{2-[4-(7-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 23 mg (27%), R_t (min) reported is for the following HPLC conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 5.725; MS (APCI), $(M+1)^+$ = 425.2.
#124	7-methoxy-3-piperazin-1-yl-benzo[d]isothiazole	1-(5-{2-[4-(7-Methoxy-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 23 mg (26%), R_t (min) reported is for the following HPLC conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 5.275; MS (APCI), $(M+1)^+$ = 437.1.
#125	5-fluoro-3-piperazin-1-yl-benzo[d]isothiazole	1-(5-{2-[4-(5-Fluoro-benzo[d]isothiazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 52 mg (57%), R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5

			mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 14.59; MS (APCI), $(M+1)^+$ = 425.2.
#126	3-piperazin-1-yl-benzo[d]isoxazole	1-{5-[2-(4-Benzo[d]isoxazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone	Yield: 21 mg (27%), R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 7.87; MS (APCI), $(M+1)^+$ = 391.1.
#127	5-fluoro-3-piperazin-1-yl-benzo[d]isoxazole	1-(5-{2-[4-(5-Fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 15 mg (18%), R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 9.699; MS (APCI), $(M+1)^+$ = 409.2.
#128	5-chloro-3-piperazin-1-yl-benzo[d]isoxazole	1-(5-{2-[4-(5-Chloro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 18 mg (21%), R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 15.722; MS (APCI), $(M+1)^+$ = 425.1.
#129	6-fluoro-3-piperazin-1-yl-benzo[d]isoxazole.	1-(5-{2-[4-(6-Fluoro-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 19 mg (23%), R_t (min) reported is for the following HPLC conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: R_t = 9.971; MS

			(APCI), $(M+1)^+ = 409.2$.
#130	7-methyl-3-piperazin-1-yl-benzo[d]isoxazole	1-(5-{2-[4-(7-Methyl-benzo[d]isoxazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 18 mg (22%), R_t (min) reported is for the following HPLC conditions: 70:30 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: $R_t = 12.705$; MS (APCI), $(M+1)^+ = 405.2$.
#131	1-benzo[b]thiophen-3-yl-piperazine	1-{5-[2-(4-Benzo[b]thiophen-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone	Yield: 24 mg (30%), R_t (min) reported is for the following HPLC conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: $R_t = 5.760$; MS (APCI), $(M+1)^+ = 406.1$.
#132	3-piperazin-1-yl-1H-indazole	1-(5-{2-[4-(1H-Indazol-3-yl)-piperazin-1-yl]-ethyl}-2,3-dihydro-indol-1-yl)-ethanone	Yield: 32 mg (41%), R_t (min) reported is for the following HPLC conditions: 60:40 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: $R_t = 2.902$; MS (APCI), $(M+1)^+ = 391$.

PREPARATION 61

5-(2-Chloro-ethyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester



To a suspension 30 g (0.286 mol) of known 5-(2-chloro-ethyl)-1,3-dihydro-indol-2-one (Lowe, John A., III; Seeger, Thomas F.; Nagel, Arthur A.; Howard, Harry R.; Seymour, Patricia A.; Heym, James H.; Ewing, Frank E.; Newman, Michael E.;

Schmidt, Anne W.; et al. 1-Naphthylpiperazine derivatives as potential atypical antipsychotic agents. *J. Med. Chem.* **1991**, *34(6)*, 1860-6) in anhydrous toluene (600 mL) was added Borane methyl sulfide complex (2.0 M in toluene, 230 mL) and the resulting mixture was refluxed for 5 hours. The mixture was cooled and saturated sodium bicarbonate (300 mL) was added. The mixture was then heated to reflux for an additional 5 hours. The organic solvent was removed *in vacuo*. To the aqueous residue was added 1,4 dioxane (300 mL), di-tert-butyl dicarbonate (42 g, 0.192 mol) and the resulting mixture was stirred for 60 hours at rt. The reaction was diluted with water, extracted with ethyl acetate, dried, concentrated and the residue was purified via flash chromatography (heptane-ethyl acetate/4:1) to afford solid. Yield: 41.6 g (96%). MS (APCI), $(M+1)^+ = 225.9$.

EXAMPLE 133

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester

A mixture of 5-(2-chloro-ethyl)-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester (27.7 g, 0.098 mol), 3-piperazin-1-yl-benzo[*d*]isothiazole hydrochloride (20.2g, 0.079 mol) and sodium carbonate (18.6 g, 0.175 mol) in 1,4-dioxane-water (320 + 560 mL) was stirred at reflux for 48 hours. Additional cesium carbonate (18 g, 0.055 mol) was added and the mixture was heated at reflux for an additional 6 hours. Mixture was cooled, diluted with water and extracted with ethyl acetate (2 x 1 L), dried and concentrated, purified via flash chromatography (heptane-ethyl acetate-triethyl amine/2:1:0.01) to provide a white powder. Yield: 26.2 g (67%). MS (APCI), $(M+1)^+ = 465.2$.

PREPARATION 62

3-{4-[2-(2,3-Dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid tert-butyl ester was dissolved in 1,4-dioxane (300 mL) and cooled to 10 °C before 1,4-dioxane-HCl (4.0N, 700mL) was added and the resulting mixture was stirred at rt overnight. The resulting white precipitate was collected via filtration. Yield: 29.5 g (95%). ^{1}H NMR (400 MHz, D_2O) δ ppm 3.02 (m, 2 H) 3.14 (t, *J*=7.69

Hz, 2 H) 3.25 (d, *J*=10.01 Hz, 4 H) 3.33 (m, 2 H) 3.56 (m, 2 H) 3.71 (t, *J*=7.69 Hz, 2 H) 3.96 (d, *J*=10.75 Hz, 2 H) 7.19 (m, 1 H) 7.28 (m, 3 H) 7.42 (t, *J*=7.69 Hz, 1 H) 7.80 (dd, *J*=16.97, 8.18 Hz, 2 H).

EXAMPLE 134

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-ethanone

A solution of 3-{4-[2-(2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (364 mg, 1.0 mmols) in THF (4.0 mL) with triethylamine (0.200 mL, 1.5 mmols) was treated with acetyl chloride (0.078 mL, 1.1 mmols) and stirred for 16 hours at rt. The reaction was quenched with sodium hydroxide (1N, 5 mL), extracted with methylene chloride and filtered through 5 µm PTFE (phase-separating filter), and concentrated in vacuo, followed by a crystallization from isopropyl alcohol to yield: 253 mg (62%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 406.9 $[M+H]^+$.

The title compounds of Examples 135 through 145 were prepared from 3-{4-[2-(2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]iso-thiazole in a parallel fashion to that reported above using the appropriate commercially available acid chloride.

EXAMPLE	ACID CHLORIDE	COMPOUND NAME	DATA
#135	propionyl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-propan-1-one	Yield: 301 mg (72%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 420.9 $[M+H]^+$.
#136	butyryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-butan-1-one	Yield: 240 mg (55%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 435.0 $[M+H]^+$.
#137	isobutyryl chloride	1-{5-[2-(4-	Yield: 165 mg (38%)

		Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-methyl-propan-1-one	Isolated in 98.4% purity @ 254 nm; LCMS (APCI) 435.0 $[M+H]^+$.
#138	cyclopropane carbonyl chloride	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclopropyl-methanone	Yield: 311 mg (72%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 432.9 $[M+H]^+$.
#139	valeryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-pentan-1-one	Yield: 158 mg (35%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 448.9 $[M+H]^+$.
#140	isovaleryl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-methyl-butan-1-one	Yield: 270 mg (60%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 448.9 $[M+H]^+$.
#141	trimethyl acetyl chloride	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2,2-dimethyl-propan-1-one	Yield: 142 mg (32%) Isolated in 96% purity @ 254 nm; LCMS (APCI) 448.9 $[M+H]^+$.
#142	cyclopentane carbonyl chloride	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclopentyl-methanone	Yield: 320 mg (70%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 460.9 $[M+H]^+$.
#143	cyclohexane carbonyl chloride	{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-cyclohexyl-methanone	Yield: 358 mg (76%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 474.9 $[M+H]^+$.
#144	benzoyl chloride	{5-[2-(4-Benzo[d]isothiazol-	Yield: 352 mg (75.2%)

		3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-phenyl-methanone	Isolated in 100% purity @ 254 nm; LCMS (APCI) 468.9 $[M+H]^+$.
#145	methane sulfonyl chloride	3-{4-[2-(1-Methanesulfonyl-2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole	Yield: 321 mg (73%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 442.9 $[M+H]^+$.

EXAMPLE 146

5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid methylamide

A solution of the product of Preparation 62, 3-{4-[2-(2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole (150 mg, 0.4 mmols in THF (5mL)) was treated by dropwise addition with above methyl isocyanate (0.03 mL) at rt and allowed to stir for 72 hours. The reaction was concentrated to dryness, diluted with H_2O and extracted with methylene chloride and filtered through 5 µm PTFE (phase-separating filter), and concentrated *in vacuo*, followed by a crystallization from acetonitrile to yield: 124 mg (74%). R_t (min) reported is for the following HPLC conditions: 65:35 [H_2O:MeCN]+0.1% TFA, 1.5 mL/min, 250x4.6 mm LUNA C_{18}. Isolated in 100% purity @ 254 nm HPLC: $R_t = 3.70$; MS (APCI), $(M+1)^+ = 422.2$.

The following compounds were prepared from 3-{4-[2-(2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole in a fashion similar to that reported above using the appropriate commercially available isocyanate.

EXAMPLE	ISOCYANATE	COMPOUND NAME	DATA
#147	ethyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid ethylamide	Yield: 120 mg (69%) Isolated in 100% purity @ 254 nm HPLC: $R_t = 4.474$; MS (APCI), $(M+1)^+ =$ 436.3.
#148	n-propyl	5-[2-(4-Benzo[d]isothiazol-3-yl-	Yield: 118 mg (66%)

	isocyanate	piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid propylamide	Isolated in 100% purity @ 254 nm HPLC: R_t = 5.864; MS (APCI), $(M+1)^+$ = 450.3.
#149	isopropyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid isopropylamide	Yield: 128 mg (71%) Isolated in 100% purity @ 254 nm HPLC: R_t = 5.834; MS (APCI), $(M+1)^+$ = 450.2.
#150	t-butyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid tert-butylamide	Yield: 109 mg (59%) Isolated in 100% purity @ 254 nm HPLC: R_t = 9.459; MS (APCI), $(M+1)^+$ = 464.3.
#151	cyclopentyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid cyclopentylamide	Yield: 179 mg (94%) Isolated in 100% purity @ 254 nm HPLC: R_t = 8.975; MS (APCI), $(M+1)^+$ = 476.2.
#152	phenyl isocyanate	5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indole-1-carboxylic acid phenylamide	Yield: 63 mg (32%) Isolated in 100% purity @ 254 nm HPLC: R_t = 13.091; MS (APCI), $(M+1)^+$ = 484.1.

EXAMPLE 153

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-chloro-ethanone

Chloroacetyl chloride was added dropwise to a solution of the product of Preparation 62, 3-{4-[2-(2,3-dihydro-1H-indol-5-yl)-ethyl]-piperazin-1-yl}-benzo[d]isothiazole in THF at 0 °C and allowed to warm to RT with stirring. The reaction was allowed to stir for 16 hours. The reaction was quenched with water and

concentrated to dryness. The crude was suspended in CH_2Cl_2 (500mL) and washed with brine (2X 100mL). The organics were dried with $MgSO_4$ and filtered. The sample was concentrated to dryness resulting in an off-white solid Yield: 4.2 g (95%) MS (APCI), $(M+1)^+ = 441.1$.

EXAMPLE 154

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-pyrrolidin-1-yl-ethanone

To a solution of 1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-chloro-ethanone (475 mg, 1.1 mmol) in DMF (8 mL) was added sodium carbonate (200 mg, 2.0 mmol) and pyrrolidine (0.125 mL, 1.5 mmol) and the reaction was warmed to 65 °C for 4.5 hours. The reacton was poured into water and extracted with methylene chloride, dried, concentrated and purified via medium pressure chromatography (15 g silica cartridge) elution with methylene chloride to methylene chloride:ethanol:ammonium hydroxide (100:8:1 over 1 hour). Recrystallization from acetonitrile yielded 181 mg (35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.67 (s, 4 H) 2.54 (m, 4 H) 2.64 (m, 4 H) 2.70 (m, 2 H) 3.07 (t, J=8.43 Hz, 2 H) 3.31 (m, 4 H) 3.42 (m, 4 H) 4.10 (t, J=8.55 Hz, 2 H) 6.99 (d, J=8.55 Hz, 1 H) 7.09 (s, 1 H) 7.41 (t, J=7.69 Hz, 1 H) 7.53 (t, J=7.57 Hz, 1 H) 7.93 (d, J=8.06 Hz, 1 H) 8.03 (d, J=8.06 Hz, 2 H), MS (APCI), $(M+1)^+ = 476.2$.

The following compounds were prepared from 1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-chloro-ethanone in a fashion similar to that reported above using the appropriate commercially available amine.

EXAMPLE	AMINE	COMPOUND NAME	DATA
#155	diethyl amine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-diethylamino-ethanone	Yield: 137 mg (29%) Isolated in 97% purity @ 254 nm; LCMS (APCI) 478.1 $[M+H]^+$.
#156	dimethyl amine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-	Yield: 158 mg (35%) Isolated In 100% purity @ 254 nm;

		piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-dimethylamino-ethanone	LCMS (APCI) 450.1 $[M+H]^+$.
#157	morpholine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-morpholin-4-yl-ethanone	Yield: 380 mg (77%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 492.1 $[M+H]^+$.
#158	piperidine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-piperidin-1-yl-ethanone	Yield: 150 mg (31%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 490.2 $[M+H]^+$.

EXAMPLE 159

1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-chloro-propan-1-one

Sample prepared in a same fashion to example above (1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-2-chloro-ethanone) treating with chloropropionyl chloride. Yield: 4.5 g (99%) MS (APCI), $(M+1)^+ = 450.0$.

The following compounds were prepared from 1-{5-[2-(4-benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-chloro-propan-1-one in a fashion similar to that reported above using the appropriate commercially available amine.

EXAMPLE	AMINE	COMPOUND NAME	DATA
#160	pyrrolidine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-pyrrolidin-1-yl-propan-1-one	Yield: 224 mg (42%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 490.1 $[M+H]^+$.
#161	diethyl amine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-	Yield: 220 mg (45%) Isolated in 100% purity @

		dihydro-indol-1-yl}-3-diethylamino-propan-1-one	254 nm; LCMS (APCI) 492.1 $[M+H]^+$.
#162	dimethyl amine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-dimethylamino-propan-1-one	Yield: 114 mg (18%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 464.1 $[M+H]^+$
#163	morpholine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-morpholin-4-yl-propan-1-one	Yield: 257 mg (51%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 506.1 $[M+H]^+$
#164	piperidine	1-{5-[2-(4-Benzo[d]isothiazol-3-yl-piperazin-1-yl)-ethyl]-2,3-dihydro-indol-1-yl}-3-piperidin-1-yl-propan-1-one	Yield: 205 mg (41%) Isolated in 100% purity @ 254 nm; LCMS (APCI) 504.4 $[M+H]^+$